Noninvasive Tests for Hepatic Fibrosis

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers transient elastography (e.g., FibroScan) medically necessary for distinguishing hepatic cirrhosis from non-cirrhosis in persons with hepatitis C or other chronic liver diseases (e.g., hereditary hemochromatosis). Performance of transient elastography more than twice per year is considered not medically necessary. Performance of transient elastography within 6 months following a liver biopsy, FibroTest-ActiTest/HCV-FibroSure is considered not medically necessary. Transient elastography is considered experimental and investigational for all other indications (e.g., detection of esophageal varices in individuals with cirrhosis, diagnosis of acute cellular rejection following liver transplantation, diagnosis of glycogenic hepatopathy, and diagnosis of portal hypertension).

Aetna considers FibroTest-ActiTest/HCV-FibroSure medically necessary for distinguishing hepatic cirrhosis from non-cirrhosis in persons with hepatitis C and other chronic liver diseases (e.g., hereditary hemochromatosis). Performance of this test more than twice per year is considered not medically necessary.
necessary. Performance of this test within 6 months following a liver biopsy or transient elastography is considered not medically necessary. This test is considered experimental and investigational for all other indications.

Aetna considers magnetic resonance elastography medically necessary for non-alcoholic steatosis (NASH). Aetna considered magnetic resonance elastography experimental and investigational for distinguishing hepatic cirrhosis from non-cirrhosis in persons with hepatitis C or other chronic liver diseases, and for all other indications (e.g., prediction of ascites in persons with chronic liver disease) because its effectiveness for these indications has not been established.

Aetna considers the Enhanced Liver Fibrosis (ELF) test medically necessary for the detection and prognosis of liver fibrosis in persons with chronic liver diseases.

Aetna considers acoustic radiation forced impulse (ARFI) experimental and investigational for distinguishing hepatic cirrhosis from non-cirrhosis in persons with hepatitis C and other chronic liver diseases, and for all other indications because its effectiveness for these indications has not been established.

Aetna considers hepatic artery resistive index for evaluation of fibrosis progression in individuals with non-alcoholic fatty liver disease (NAFLD) experimental and investigational because its effectiveness for this indication has not been established.

Aetna considers the following serum marker tests experimental and investigational for detecting or monitoring hepatic fibrosis in persons with hepatitis C or other chronic liver diseases (e.g., NAFLD) because their effectiveness for these indications has not been established: (not an all-inclusive list)

- Angiotensin converting enzyme
Noninvasive Tests for Hepatic Fibrosis

- FibroMAX
- FibroSpect
- HepaScore
- LIVERFAST
- Micro-fibrillar associated glycoprotein 4 (MFAP4)
- MicroRNA-21
- miR-29a and miR-122
- miRNA-221 and miRNA-222
- NASH FibroSure
- Plasma cytokeratin-18
- Signal-induced proliferation-associated 1 like 1 (SIPA1L1).

Background

Hepatic fibrosis is the excessive accumulation of fibrotic connective tissue resulting from prolonged inflammation and progressive scarring of the liver due to a sustained wound-healing response to alcohol or nonalcohol-induced liver injury (nonalcoholic liver disease includes, but not limited to, hepatitis B and hepatitis C infections). The increased fibrosis and liver stiffness reduces blood flow through the liver, which leads to hardening and death of liver cells. Other chronic liver diseases include alcoholic liver disease, chronic hepatitis B, non-alcoholic steatosis, and chronic viral hepatitis B.

Liver biopsy is considered the gold standard for diagnosis and management of chronic liver disease. However, it is an invasive procedure that may result in complications. For that reason, non-invasive hepatic fibrosis tests are being introduced. Examples of these tests include, but may not be limited to, the following:

Serum Markers of Hepatic Fibrosis
Liver fibrosis serum panels are blood serum laboratory tests that have been developed as an alternative to liver biopsy to purportedly determine the extent of liver damage that has occurred in individuals with liver disease, such as hepatitis C virus (HCV).

Biochemical marker combinations are being developed as alternatives to liver biopsy in patients with chronic hepatitis C and other chronic liver diseases, including chronic hepatitis B, alcoholic liver disease, or non-alcoholic steatosis. Non-invasive tests are being developed to replace liver biopsy, and thus avoid the risk of biopsy-related adverse events. Non-invasive tests also have the potential to avoid limitations of liver biopsy, including the risk of sampling errors and inter- and intra-pathologist variability.

An assessment by the Belgian Healthcare Knowledge Center (KCE, 2016) reported that until recently, the usual examination to establish the degree of hepatic fibrosis was a histopathological examination of a liver sample taken by means of a liver biopsy. The result of a biopsy is expressed on the basis of the METAVIR scoring system which qualifies the degree of liver fibrosis in function of the histologic characteristics (F score) and the degree of inflammatory activity (A score) observed in the sample. The assessment noted, however, that liver biopsy is an invasive test which carries a risk of bleeding, especially in patients in an advanced stage of the illness. The assessment noted that there are now a number of non-invasive tests for hepatic fibrosis. However, there are no studies that measure the long-term outcomes of patients managed with these non-invasive tests (the longest study ran over a 9-year period but was conducted on a relatively small sample). The only studies available are cross-sectional studies which evaluate the sensitivity and specificity of these non-invasive tests in comparison with biopsies.
The FibroSpect II (Prometheus Laboratories, San Diego, CA) is a non-invasive diagnostic panel to assist in the detection of liver fibrosis. The FibroSpect II uses a combination of components in the fibrogenic cascade, such as hyaluronic acid, TIMP-1 (tissue inhibitor of metalloproteinase), and alpha-2-macroglobulin. Using an algorithm, the results of the measurements are converted into a score to determine an individual's fibrosis score. The test is intended to differentiate mild fibrosis from more severe disease.

HepaScore measures four markers for liver fibrosis -- bilirubin, gamma glutamyl transpeptidase, hyaluronic acid, and alpha-2 macroglobulin -- and applies the results to an algorithm, combined with an individual’s age and sex, to determine a liver fibrosis score.

Non-alcoholic fatty liver disease (NAFLD) fibrosis score is based on analytes that are supposedly individually useful for evaluating patients with liver disease. The test includes ALT, albumin, aspartate aminotransferase (AST) glucose and platelet count. Age and body mass index (BMI) are also used to calculate the fibrosis score.

The FibroTest (Biopredictive, Houilles, France) and the ActiTest (Biopredictive, Houilles, France), marketed in the United States as the HCV-FibroSure Test (LabCorp, Burlington, NC) (also known as HCV-FibroSure, ASH FibroSure, NASH FibroSure) are serum biochemical tests for the assessment of fibrosis and necroinflammatory activity, respectively. The HCV-FibroSure Test includes the following five markers, as well as age and gender: alpha2-macroglobulin, haptoglobin, gamma-glutamyl transpeptidase (GGT), total bilirubin, apolipoprotein A1, plus alanine aminotransferase (ALT). These measurements are applied to an algorithm, combined with an individual’s age and sex, to determine liver fibrosis severity. In addition, ASH FibroSure
and NASH FibroSure purportedly provide markers for steatosis, alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) as well as for liver fibrosis.

Rossi et al (2003) reported on the results of FibroTest scores of 125 patients with hepatitis C. Of these, 57 had FibroTest scores either less than 0.1 (indicating no fibrosis) or greater than 0.6 (indicating significant fibrosis). Although 33 of the 125 patients had FibroTest scores of less than 0.1 and were therefore deemed unlikely to have fibrosis, 6 (18%) had significant fibrosis. Conversely, of the 24 patients with scores of greater than 0.6 who were likely to have significant fibrosis, 5 (21%) had mild fibrosis. The investigators concluded that, "[o]f the 125 patients in the cohort, 57 (46%) could have avoided liver biopsy"; but discrepant results were recorded in 11 of those 57 (19%). In other words, discrepancies with the biopsy gold standard were found in one-fifth of patients. There are no prospective clinical outcome studies of the HCV-FibroSure in the management of patients with hepatitis C or other chronic liver diseases.

An National Institutes of Health Consensus Statement on Management of Hepatitis C (NIH, 2002) concluded that liver biopsy is useful in defining baseline abnormalities of liver disease and in enabling patients and healthcare providers to reach a decision regarding antiviral therapy. The NIH Consensus Statement concludes that noninvasive tests are not adequate substitutes for liver biopsy.

Various noninvasive tests of hepatic fibrosis have been examined for monitoring patients with chronic hepatitis C virus (HCV) infection. These include routinely available laboratory tests, such as liver-associated chemistries, platelet count, and prothrombin time, as well as specific serum markers of fibrosis and inflammation not currently widely available or well validated. No single test or panel of serologic markers can provide an accurate assessment of intermediate stages of hepatic fibrosis. Similarly, quantitative tests of liver function
and radiologic imaging of the liver are sensitive for diagnosing advanced cirrhosis but are not useful in assessing hepatic fibrosis and early cirrhosis.

In a review on newer markers for hepatocellular carcinoma, Marrero and Lok (2004) stated that there is a scarcity of longitudinal studies evaluating the ability of biomarkers to detect pre-clinical disease. There is an urgent need for novel biomarkers for the detection of early hepatocellular carcinoma.

Suzuki et al (2005) stated that "use of an accurate serum marker for severe hepatic fibrosis may also improve accuracy of non-invasive diagnostic models. Hyaluronic acid, a serum marker for severe hepatic fibrosis, has been reported to have a high diagnostic performance in assessing the severity of hepatic fibrosis in patients with alcoholic liver disease. In this issue, a non-invasive diagnostic model including hyaluronic acid was shown to have excellent performance in excluding the presence of medium to large esophageal varices in severe alcohol abusers. Based on current evidence, the strategy of using a non-invasive diagnostic model together with a serum marker for severe hepatic fibrosis may improve cost-benefit in the prevention of variceal hemorrhage among patients with alcoholic liver disease. The independent verification of such diagnostic models is needed".

Evidence based guidelines on the management of hepatitis C from the American Association for the Study of Liver Diseases (Strader et al, 2004) stated: "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".
Serum gamma glutamyltransferase (GGT) is elevated in individuals with acute and chronic alcohol toxicity. Serum GGT assay may be useful in evaluating patients when heavy drinking is suspected but the patient denies it (NIAAA, 2005).

Wilson et al (2006) stated that although most HCV infections are acquired by injection drug use, prospective data on the progression of liver fibrosis are sparse. In this study, baseline liver biopsies were obtained on a random sample of 210 out of 1,667 HCV-positive injection drug users (IDUs). Subjects were followed biannually, with a second biopsy offered to those eligible. Paired biopsies were scored 0 to 6 (modified Ishak score), significant fibrosis was defined as score 3 or greater, and progression of fibrosis was defined as an increase 2 or more units or clinical evidence of end-stage liver disease. Predictive values of blood markers (FibroSure, aspartate aminotransferase-to-platelet-ratio index (APRI) and alanine aminotransferase (ALT)) were assessed for detection of contemporaneous and future liver fibrosis. Among 119 prospectively followed IDUs, 96% were African American; 97% HCV genotype 1a/b; 27% HIV-infected, and median age was 42 years. Most (90.7%) did not have significant liver fibrosis at first biopsy. Although predictive value for detecting insignificant fibrosis at first biopsy was greater than 95% for FibroSure, APRI, and ALT, specificities were 88.9%, 72.7%, and 72.7%, respectively. After 4.2 years median follow-up, 21% had progression of fibrosis, which was significantly associated with serum level of HCV RNA and ALT. No serological test had predictive value greater than 40% for contemporaneous or future significant fibrosis. Even initial biopsy result had only a 30.4% value for predicting future significant fibrosis. The authors concluded that significant liver fibrosis and progression were detected in some, but not most, IDUs in this cohort. In this setting with low fibrosis prevalence, FibroSure, ALT, and APRI tests predict insignificant fibrosis; however, further work is needed to find non-invasive markers of significant liver fibrosis.
Nouri and Pockros (2007) noted that biochemical markers are a potentially useful alternative to liver biopsy in patients with chronic hepatitis C aged 65 years and older. Furthermore, Rossi et al (2007) stated that an obstacle to widespread adoption of serum marker models (e.g., FibroSpect) for assessing liver fibrosis has been the lack of uniform performance indicators, such as diagnostic odds ratios and likelihood ratios. At present, serum marker models are not considered sufficiently reliable to replace liver biopsy in patients with chronic liver disease.

Shaheen and Myers (2008) performed a systematic review and meta-analysis of the diagnostic accuracy of fibrosis marker panels in patients with HIV/hepatitis C coinfection. Random effects meta-analyses and areas under summary receiver operating characteristics curves (AUC) examined test accuracy for detecting significant fibrosis (F2 to F4) and cirrhosis. Heterogeneity was explored using meta-regression. Five studies (n = 574) including 4 fibrosis measures (APRI [n = 4 studies], Forns’ [n = 2], FibroTest [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% confidence interval [CI]: 0.78 to 0.86) and diagnostic odds ratio was 7.8 (5.1 to 11.9). For cirrhosis, these figures were 0.83 (0.69 to 0.97) and 11.0 (4.6 to 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 concluded 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. They noted that additional studies are needed to identify the optimal measure.
Smith and Sterling (2009) reviewed non-invasive measures and their ability to replace biopsy for assessing hepatic fibrosis in patients with chronic HCV. A systematic review of PUBMED and EMBASE was carried out through 2008 using the following search terms: HCV, liver, elastography, hepatitis, Fibroscan, SPECT, non-invasive liver fibrosis, ultrasonography, Doppler, MRI, Fibrotest, Fibrosure, Actitest, APRI, Forns and breath tests, alone or in combination. These investigators identified 151 studies: 87 using biochemical, 57 imaging and 7 breath tests either alone or in combination. The authors concluded that great strides are being made in the development of accurate non-invasive methods for determination of fibrosis. Although no single non-invasive test or model developed to date can match that information obtained from actual histology (i.e., inflammation, fibrosis, steatosis), combinations of 2 modalities of non-invasive methods can reliably differentiate between minimal and significant fibrosis, and thereby avoid liver biopsy in a significant percentage of patients.

Carlson and colleagues (2009) evaluated the clinical and economic outcomes of non-invasive testing strategies in the diagnosis of significant liver fibrosis (Metavir score greater than or equal to 2) compared with liver biopsy. These researchers developed a decision analytic model of non-invasive testing strategies in a hypothetical patient population with genotype 1 hepatitis C virus infection, with no contraindications to liver biopsy. The testing strategies included a testing algorithm using the Fibrosure test, a non-invasive measure of fibrosis, followed by liver biopsy for patients with indeterminate results, Fibrospect II, and Fibroscan. The primary outcomes were sensitivity, specificity, diagnostic accuracy (true positive + true negatives/total patients), and costs, evaluated from the health-care payer perspective. The testing algorithm using Fibrosure was the most accurate non-invasive strategy with a sensitivity, specificity, and overall accuracy of 84%, 87%, and 86%, respectively. In comparison with liver biopsy alone, there was
a cost savings of approximately $770/person with the Fibrosure testing algorithm, but a net decrease in accuracy of 14%. Fibroscan II and Fibroscan had poorer accuracy (decreases of 12% and 4%, respectively) and lower costs (-$138 and -$357, respectively) compared with the Fibrosure algorithm. In uncertainty analyses in which biopsy sampling error was considered, the Fibrosure algorithm remained consistently less accurate (5 to 14% decrease). The authors concluded that the results of this study suggested that compared with liver biopsy, non-invasive testing algorithms can result in short-term cost savings, but the consequences of misdiagnosis in terms of health outcomes and treatment costs might out-weigh the short-term gains in cost and convenience.

Adams (2011) stated that fibrosis prediction is an essential part of the management of patients with chronic liver disease. Serum biomarkers offer a number of advantages over the traditional standard of fibrosis assessment of liver biopsy, including safety, cost-savings and wide spread accessibility. Current biomarker algorithms include indirect surrogate measures of fibrosis, including aminotransaminases and platelet count, or direct measures of fibrinogenesis or fibrinolysis such as hyaluronic acid and tissue inhibitor of metalloproteinase-1. A number of algorithms have now been validated across a range of chronic liver disease including chronic viral hepatitis, alcoholic and non-alcoholic fatty liver disease. Furthermore, several models have been demonstrated to be dynamic to changes in fibrosis over time and are predictive of liver-related survival and overall survival to a greater degree than liver biopsy. Current limitations of biomarker models include a significant indeterminate range, and a predictive ability that is limited to only a few stages of fibrosis. Utilization of these biomarker models requires knowledge of patient co-morbidities which may produce false positive or negative results in a small proportion of individuals. Furthermore, knowledge of the underlying prevalence of fibrosis in the patient population is required for interpretation of the positive or negative predictive values of a test result.
Novel proteins identified by proteomic technology and genetic polymorphisms from genome association studies offer the possibility for further refinement and individualization of biomarker fibrosis models in the future.

Sebastiani and associates (2011) examined the effect of etiology and stages of hepatic fibrosis on the performance of fibrosis biomarkers. A total of 2,411 patients with compensated chronic liver disease (CLD) (hepatitis C virus [HCV] = 75.1%, hepatitis B virus [HBV] = 10.5%, non-alcoholic steato-hepatitis [NASH] = 7.9%, HIV/HCV = 6.5%) were consecutively enrolled in 9 centers. APRI, Forns' index, Lok index, AST-to-ALT ratio, Fib-4, platelets and Fibrotest-Fibrosure were tested against liver biopsy, considered the gold standard. The effect of the stages of hepatic fibrosis to diagnose significant fibrosis and cirrhosis (greater than or equal to F2 and F4, respectively) was investigated through difference between advanced and non-advanced fibrosis stages (DANA). Performance was expressed as observed area under the receiver-operating characteristic (ROC) curve (ObAUROC) and AUROC adjusted for DANA (AdjAUROC). Performance of APRI and Fibrotest-Fibrosure was higher than other biomarkers. In all etiologies, AdjAUROC was higher than ObAUROC. APRI showed its best performance in HCV mono-infected cases, with an AdjAUROC of 0.77 and 0.83 for greater than or equal to F2 and F4, respectively. In HBV and NASH patients, its performance was poor (AdjAUROC < 0.70). Performance of Fibrotest-Fibrosure was good in all etiologies for both greater than or equal to F2 and F4 (AdjAUROC > 0.73), except for greater than or equal to F2 in NASH (AdjAUROC = 0.64). Performance of all biomarkers was reduced in HCV cases with normal ALT. The authors concluded that etiology is a major factor influencing the performance of liver fibrosis biomarkers. Even after correction for DANA, APRI and Fibrotest-Fibrosure exhibit the best performance. However, liver biopsy is not replaceable, especially to diagnose greater than or equal to F2 and in HCV carriers with normal ALT.
Adams et al (2005) stated that staging hepatic fibrosis by liver biopsy guides prognosis and treatment of hepatitis C, but is invasive and expensive. These researchers sought to create an algorithm of serum markers that accurately and reliably predict liver fibrosis stage among hepatitis C patients. A total of 10 biochemical markers were measured at time of liver biopsy in 117 untreated hepatitis C patients (training set). Multi-variate logistic regression and ROC curve analyses were used to create a predictive model for significant fibrosis (METAVIR F2, F3, and F4), advanced fibrosis (F3 and F4), and cirrhosis (F4). The model was validated in 104 patients from other institutions. A model (HepaScore) of bilirubin, gamma-glutamyltransferase, hyaluronic acid (HA), alpha(2)-macroglobulin, age, and sex produced areas under the ROC curves (AUCs) of 0.85, 0.96, and 0.94 for significant fibrosis, advanced fibrosis, and cirrhosis, respectively. In the training set, a score greater than or equal to 0.5 (range of 0.0 to 1.0) was 92 % specific and 67 % sensitive for significant fibrosis, a score of less than 0.5 was 81 % specific and 95 % sensitive for advanced fibrosis, and a score of less than 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 greater than or equal to 0.5 provided a specificity and sensitivity of 89 % and 63 % for significant fibrosis, whereas scores less than 0.5 had 74 % specificity and 88 % sensitivity for advanced fibrosis, respectively. The authors concluded that a model of 4 serum markers plus age and sex provides clinically useful information regarding different fibrosis stages among hepatitis C patients.

Ngo, et al. (2006) compared the 5-year prognostic value of the FibroTest with biopsy staging for predicting cirrhosis decompensation and survival in patients with chronic HCV infection. Fibrosis stage was assessed on the same day by FibroTest and biopsy in a prospective cohort of 537 patients. Disease classification at baseline was 157 patients with severe fibrosis (FibroTest >0.58), 137 with moderate fibrosis.
(FibroTest 0.32-0.58), and 243 with no or minimal fibrosis (FibroTest <0.32). In 64 untreated patients with severe fibrosis, survival without HCV complications was 73% [95% confidence interval (CI), 59%-86%; 13 complications], and survival without HCV-related death was 85% (95% CI, 73%-96%; 7 HCV deaths). Survival rates were higher in patients with moderate fibrosis, [99% (95% CI, 97%-100%; 1 complication; P <0.001) and 100% (no HCV death; P <0.001) for patients with and without HCV-related complications, respectively], and in patients with minimal fibrosis [100% (no complication; P <0.001 vs severe) and 100% (no HCV death; P <0.001 vs severe), respectively]. FibroTest was a better predictor than biopsy staging for HCV complications, with area under the ROC curves (AUROC) = 0.96 (95% CI, 0.93%-0.97%) vs 0.91 (95% CI, 0.85%-0.94%; P = 0.01), respectively; it was also a better predictor for HCV deaths: AUROC = 0.96 (95% CI, 0.93%-0.98%) vs 0.87 (95% CI, 0.70%-0.94%; P = 0.046), respectively. The prognostic value of FibroTest was still significant (P <0.001) in multivariate analyses after taking into account histology, treatment, alcohol consumption, and HIV coinfection.

Cacoub, et al. (2008) compared non-invasive biological liver fibrosis scores, as alternatives to liver biopsy, in HIV/HCV co-infected patients. Two hundred and seventy-two HIV/HCV patients, naive for HCV treatment, underwent liver biopsy [197 (72%) men, 39.9 years, fibrosis stage (Metavir) F1 (25%), F2 (40%), F3 (25%), F4 (10%), median CD4 486/mm^3 and median HIV viral load 3.5 log. Fibrotest (FT), Hepascore (HS), Fibrometer (FM), SHASTA, APRI, Forns index, and Fib-4 were tested in order to differentiate patients with mild to moderate fibrosis (F2) and those with advanced fibrosis (F3). The AUROC and the rate of well-classified patients were compared to liver biopsy. FT, HS, and FM were able to stage liver fibrosis in all patients with AUROCs of 0.78, 0.84 and 0.89 for the diagnosis of F2, respectively. The correlation coefficient indexes were 0.37, 0.46 and 0.48, respectively. The rates of well-classified patients were 62%,
68% and 71%, respectively. Fib-4, APRI and the Forn's index were only able to stage 37-61% of patients and showed lower accuracies. Using a combination of FT, HS and FM did not significantly increase the performance of each test. The investigators concluded that, in HIV/HCV co-infected patients, Fibrometer, Hepascore and Fibrotest outperformed other non-invasive liver fibrosis biomarkers for the prediction of significant liver fibrosis.

Halfon, et al. (2008) updated a previous meta-analysis of Fibrotest (FT) diagnostic value. For diagnostic value, the main endpoint was the FT area under the ROC curves (AUROCs) for the diagnosis of bridging fibrosis (F2/F3/F4 vs F0/F1), standardized for the spectrum of fibrosis. Sensitivity analysis integrated the non-standardized observed AUROCs, the independency of authors, size (length) of biopsy, prospective design, correctness of procedures, co-morbidities, and timelag between biopsy and serum sampling. For prognostic value, the main endpoint was the FT AUROC for the prognostic value of liver complications or death related to liver disease. A total of 38 diagnostic studies were included, which pooled 7985 subjects who had undergone both FT and biopsy (4600 HCV, 1580 HBV, 267 NAFLD, 524 ALD and 1014 mixed). The mean standardized AUROC was 0.84 (95% CI, 0.83-0.86), with no differences in terms of causes of liver disease: HCV 0.84 (0.82-0.87); HBV 0.81 (0.78-0.83); NAFLD 0.84 (0.76-0.92); ALD 0.87 (0.82-0.92); and mixed 0.85 (0.81-0.89). Three prognostic studies were also included. FT was found to have higher or similar prognostic value compared with biopsy in patients with chronic hepatitis C (CHC), CHB or ALD.

Stevenson et al (2012) evaluated the diagnostic accuracy, cost-effectiveness, and effect on patient outcomes of 4 non-invasive tests for liver fibrosis [the Enhanced Liver Fibrosis (ELF) test (Siemens Healthcare Diagnostic Inc., Tarrytown, NY), FibroTest (BioPredictive, Paris, France), FibroMAX (BioPredictive, Paris, France) and transient elastography (FibroScan; produced by EchoSens, Paris, France and
distributed in the United Kingdom. by Artemis Medical Ltd, Kent, UK) in patients suspected of having ALD. A systematic review was undertaken to identify studies reporting the diagnostic and prognostic accuracy of the ELF test, FibroTest, FibroMAX, and FibroScan for the identification of liver fibrosis and associated conditions in patients with suspected ALD. The following databases were searched in January 2010: MEDLINE (from 1950 to January 2010), MEDLINE In-Process & Other Non-Indexed Citations (from 1950 to January 2010), EMBASE (from 1980 to January 2010), Cochrane Database of Systematic Reviews (from 1996 to January 2010), Cochrane Central Register of Controlled Trials (from 1898 to January 2010), Cochrane Methodology Register (from 1904 to January 2010), Database of Abstracts of Reviews of Effects (from 1995 to January 2010), HTA Database (from 1995 to January 2010), NHS Economic Evaluation Database (from 1995 to January 2010), Cumulative Index to Nursing and Allied Health Literature (from 1982 to January 2010), Web of Knowledge and Science Citation Index (from 1969 to January 2010).

Study quality was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist. Owing to the heterogeneity of the studies, no formal meta-analysis was undertaken. A de novo mathematical model was constructed to estimate the incremental costs and incremental quality-adjusted life-years (QALYs) associated with alternative strategies compared with a biopsy-all strategy. The tests were assessed first as a replacement for liver biopsy, and secondly as an additional test prior to liver biopsy. A total of 36 scenarios were assessed for each non-invasive test strategy, which varied the sensitivity of biopsy, the anxiety associated with biopsy, sensitivity and specificity values and whether or not the biopsy was percutaneous or transjugular. For each scenario, threshold levels were reported where biopsying all patients was more cost-effective than the strategy for 2 parameters (the decreased level of abstinence associated with the strategy compared with biopsying all and the level of incidental QALY gain associated with biopsy). No studies were identified that specifically assessed the ELF test,
although a study was identified that evaluated the diagnostic accuracy of the European Liver Fibrosis Test (essentially, the ELF test with the addition of age to the algorithm) compared with biopsy. Three studies of FibroTest, no relevant studies of FibroMAX, and 6 studies of FibroScan assessing accuracy compared with biopsy in patients with known or suspected alcohol-related liver disease were identified. In all studies, the number of patients with suspected ALD was small, meaning that the estimated sensitivities and specificities were not robust. No conclusive estimate of the cost per QALY of each non-invasive test could be provided. Scenarios exist in which each of the strategies analyzed is more cost-effective than biopsying all patients and, in contrast, scenarios exist in which each strategy is less cost-effective than biopsying all patients. The authors concluded that no conclusive result can be provided on the most cost-effective strategy until further data are available. A large number of parameters require data; however, the following were selected as being of most importance: (i) the sensitivity and specificity of each non-invasive liver test (NILT) against biopsy at validated and pre-selected cut-off thresholds; (ii) the influence of potential confounding variables such as current drinking behavior and the degree of hepatic inflammation on the performance of NILTs; and (iii) the likelihood, and magnitude, of decreases in abstinence rates associated with a diagnosis of significant ALD by diagnostic modality and the incidental gains in QALYs that may be associated with biopsy.

Sebastiani and Alberti (2012) chronic hepatitis C represents a major cause of progressive liver disease that can eventually evolve into cirrhosis and its end-stage complications. Formation and accumulation of fibrosis in the liver is the common pathway that leads to evolutive liver disease. Precise staging of liver fibrosis is essential for patient management in clinical practice because the presence of bridging fibrosis represents a strong indication for anti-viral therapy, while
cirrhosis requires a specific follow-up. Liver biopsy has always represented the standard of reference for assessment of hepatic fibrosis, but it has limitations: it is invasive, costly and prone to sampling errors. Recently, blood markers and instrumental methods have been proposed for the non-invasive assessment of liver fibrosis in hepatitis C. However, international guidelines do not recommend the widespread use of non-invasive methods for liver fibrosis in clinical practice. This is because, in some cases, unsatisfactory accuracy and incomplete validation of others. Some studies suggested that the effectiveness of non-invasive methods for assessing liver fibrosis may increase when they are combined, and a number of sequential and synchronous algorithms have been proposed for this purpose, with the aim of reducing rather than substituting liver biopsies. This may represent a rational and reliable approach for implementing noninvasive assessment of liver fibrosis in clinical practice. It could allow more comprehensive first-line screening of liver fibrosis in hepatitis C than would be feasible with liver biopsy alone.

Usluer et al (2012) compared the results of 9 non-invasive serum biomarkers with liver biopsies to predict liver fibrosis stage. HCV-RNA-positive, HCV genotype 1, treatment-naive patients with chronic HCV infections were included from 14 centers (n = 77). The platelet count, AST/ALT ratio (AAR), cirrhosis discriminate score (CDS), FIB4, APRI, age-platelet (AP) index, Goteborg University cirrhosis index (GUCI), FibroTest, and ActiTest were calculated and compared to histologic findings. All serum biomarkers, except AAR, were weakly or moderately correlated with liver biopsy results (ISHAK fibrosis score). The mean scores of FibroTest, FIB4, APRI, and AP index were significantly different between F0-F2 and F3-F4 groups and the negative predictive values (NPVs) of the F3-F4 group were 95 %, 85 %, 85 %, and 83 %, respectively, for these serum biomarkers. The authors concluded that these findings suggested that serum biomarkers may help to diagnose significant fibrosis but inadequate to detect fibrosis in early stages.
Bhogal and Sterling (2012) noted that several blood tests, algorithms, and imaging tests have been studied as non-invasive markers to stage fibrosis in hepatitis C. In patients without suspicion for cirrhosis, 2 non-invasive methods can be used to predict presence of absence of significant liver fibrosis; however, liver biopsy remains the gold standard.

Chladek et al (2013) compared the results of serial measurements of serum fibrosis markers during the remission-induction phase of treatment with methotrexate (MTX) to those of patients on biological therapy and long-term MTX therapy (greater than 2 years). Serum concentrations of HA, N-terminal propeptide of collagen type III (PIIINP) and the results of 2 multi-test algorithms FibroTest and HepaScore were evaluated in patients with chronic plaque psoriasis (n = 24, age: 28 to 79 years, baseline Psoriasis Area Severity Index [PASI] 13.5, range of 2.2 to 33) at baseline and weeks 16 and 26 after the start of pharmacokinetically-guided therapy with MTX (Group A). Patients on established therapy with biologics (n = 15, Group B) and long-term MTX users (n = 10, Group C) with the mean baseline PASI scores of 0.9 and 1.2 were studied in parallel cohorts. At baseline, HA, HepaScore and PIIINP were correlated with PASI of Group A patients. At weeks 16 and 26, HA decreased by 48 % and 40 % (p < 0.001) and HepaScore by 31 (p < 0.01) and 20 % (p < 0.05) respectively. PASI75 (greater than or equal to 75 % improvement from baseline PASI) was observed in 76 % of Group A patients by week 26 and the absolute decreases in PASI and both fibrosis markers were correlated (HA: r = 0.49, p = 0.018, HepaScore: r = 0.47, p = 0.022). In contrast, no significant within-group differences were found in HA and HepaScore results of patients in the groups B and C. PIIINP and FibroTest were stable in all groups. The authors concluded that the fibrosis markers HA and HepaScore (the multiple test algorithm that includes HA) are less liver specific and more prone to reflect psoriasis activity than PIIINP and FibroTest.
Salkic et al (2014) systematically reviewed studies describing the diagnostic accuracy of Fibrotest (FT) for predicting chronic hepatitis B (CHB)-related fibrosis. MEDLINE and EMBASE searches and hand searching methods were performed to identify studies that assessed the diagnostic accuracy of FibroTest in HB patients using LB as a reference standard. The investigators used a hierarchical summary receiver operating curves model and the bivariate model to produce summary receiver operating characteristic curves and pooled estimates of sensitivity and specificity. The investigators included 16 studies (N=2494) and 13 studies (N=1754) in the heterogenous metaanalysis for liver fibrosis and cirrhosis, respectively. The area under the hierarchical summary receiver operating curve for significant liver fibrosis and for all included studies was 0.84 (95% confidence interval (CI): 0.78-0.88). At the FT threshold of 0.48, the sensitivity, specificity, and diagnostic odds ratio (DOR) of FT for significant fibrosis were 61 (48-72%), 80 (72-86%), and 6.2% (3.3-11.9), respectively. The area under the hierarchical summary receiver operating curve for liver cirrhosis and for all included studies was 0.87 (95% CI: 0.85-0.90). At the FT threshold of 0.74, the sensitivity, specificity, and DOR of FT for cirrhosis were 62 (47-75%), 91 (88-93%), and 15.7% (8.6-28.8), respectively. The authors concluded that FibroTest is of value in exclusion of patients with CHB-related cirrhosis, but has suboptimal accuracy in the detection of significant fibrosis and cirrhosis. It is necessary to further improve the test or combine it with other noninvasive modalities in order to improve accuracy.

Chou and Wasson (2013) stated that many blood tests have been proposed as alternatives to liver biopsy for identifying fibrosis or cirrhosis. These investigators evaluated the diagnostic accuracy of blood tests to identify fibrosis or cirrhosis in patients with HCV infection. Data sources included MEDLINE (1947 to January 2013), the Cochrane Library, and reference lists. Studies that compared the diagnostic accuracy of blood tests with that of liver biopsy were selected.
Investigators abstracted and checked study details and quality by using pre-defined criteria. A total of 172 studies evaluated diagnostic accuracy. For identifying clinically significant fibrosis, the platelet count, age-platelet index, APRI, FibroIndex, FibroTest, and Forns index had median positive likelihood ratios of 5 to 10 at commonly used cut-offs and areas under the ROC curve (AUROCs) of 0.70 or greater (range of 0.71 to 0.86). For identifying cirrhosis, the platelet count, age-platelet index, APRI, and HepaScore had median positive likelihood ratios of 5 to 10 and AUROCs of 0.80 or greater (range of 0.80 to 0.91). The GUCI and the Lok index had slightly lower positive likelihood ratios (4.8 and 4.4, respectively). In direct comparisons, the APRI was associated with a slightly lower AUROC than the FibroTest for identifying fibrosis and a substantially higher AUROC than the aspartate aminotransferase-alanine aminotransferase ratio for identifying fibrosis or cirrhosis. The authors concluded that many blood tests are moderately useful for identifying clinically significant fibrosis or cirrhosis in HCV-infected patients. Drawbacks of this study included only English-language articles were included, and most studies had methodological limitations, including failure to describe blinded interpretation of liver biopsy specimens and inadequate description of enrollment methods.

Rossi et al (2013) noted that serum HA and biochemical models that require HA analysis are commonly used as predictors of liver fibrosis in patients with chronic liver disease, however biological variation data for HA are deficient. Four serial serum samples were obtained at weekly intervals from healthy volunteers and patients with chronic hepatitis B, chronic hepatitis C and non-alcoholic fatty liver disease (NAFLD) (20 in each group). The within-individual week-to-week variation (CVI) and reference change values for HA, α₂-macroglobulin and HepaScore were obtained. HepaScore was calculated from HA, α₂-macroglobulin, bilirubin and γ-glutamyltransferase activity. Hyaluronic acid displayed large within-individual variation, the CVI values were 62% in healthy
subjects, 38% in hepatitis C, 37% in hepatitis B, and 36% in NAFLD patients. HepaScore CVIs were 43% in healthy subjects, 24% in hepatitis C, 28% in hepatitis B, and 39% in NAFLD patients. Moreover, α₂-Macroglobulin was much less variable with CVIs ranging from 4.4% to 7.6%. Bland-Altman plots of week-to-week variations showed rates of significant disagreement for samples collected in any 2 successive weeks varied from 5% in NAFLD patients to 8.3% in healthy subjects. The authors concluded that when using non-fasting serum samples, HA and to a lesser extent, the HepaScore model displayed large within-individual variations in both health and chronic liver disease. This information is critical for interpreting the significance of both single measurements and changes in serial measurements.

Grattagliano et al (2013) stated that the diagnostic utilities of ultrasonography (US), fatty liver index (FLI) and an algorithm of 9 serum markers (FibroMAX) were evaluated in family practice to non-invasively characterize patients with NAFLD. A multi-center study was conducted by enrolling 259 consecutively observed patients (age of 51 +/- 10 years) with clinical and ultrasonographic features of NAFLD. Patients had mild (16.2%), moderate (69.9%), or severe (13.9%) liver steatosis and 60.2% had hyper-transaminasemia. The percent of patients with overweight, obesity, diabetes, hypertension, and dyslipidemia were 42.7%, 46.5% (4.2% severe obesity), 24.7%, 40.9%, and 56.4%, respectively. Lean patients (10.8%) had normal transaminases in 2/3 of the cases. A multi-variate logistic regression (including age greater than 50 years, body mass index (BMI) greater than 30 kg/m², homeostasis model assessment (HOMA) greater than 3, and hyper-transaminasemia) identified 12.3% of patients at risk for steatohepatitis. With a sensitivity of 50% and specificity of 94.7%, FibroMAX identified 34 patients (13.1%) with likely advanced fibrosis and found that over 28% of patients with moderate (ultrasonographic) steatosis were likely to be carrying severe steatosis. Steatotest score was significantly associated with BMI, waist circumference, ALT,
triglycerides, and FLI. FibroTest correlated only with ALT. Fatty liver index identified 73.4% of patients as likely to be carrying a fatty liver. The authors concluded that NAFLD should be systematically searched and characterized in all patients with metabolic disturbances and cardiovascular risk. Asymptomatic subjects at risk also should be screened for NAFLD. They stated that FibroMAX is a promising non-invasive diagnostic tool in family medicine for identifying patients at risk for NAFLD who require targeted follow-up.

Xu et al (2014) conducted a systematic review on records in PubMed, EMBASE and the Cochrane Library electronic databases, up until April 1st, 2013, in order to systematically assess the effectiveness and accuracy of these biomarkers for predicting HBV-related fibrosis. The questionnaire for quality assessment of diagnostic accuracy studies (QUADAS) was used. Out of 115 articles evaluated for eligibility, 79 studies satisfied the pre-determined inclusion criteria for meta-analysis. The authors final data set for the metaanalysis contained 30 studies. The areas under the SROC curve for APRI, FIB-4, and FibroTest of significant fibrosis 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 (P=0.0211), and for cirrhosis was affected by etiology (P=0.0159). Based on the analysis the authors concluded that FibroTest has excellent diagnostic accuracy for identification of HBV-related significant fibrosis and cirrhosis. FIB-4 has modest benefits and may be suitable for wider scope implementation.

In their review, Mato et al (2019) stated nonalcoholic fatty liver disease (NAFLD) is a heterogeneous and complex disease that is imprecisely diagnosed by liver biopsy. NAFLD covers a spectrum that ranges from simple steatosis, nonalcoholic steatohepatitis (NASH) with varying degrees of fibrosis, to
cirrhosis, which is a major risk factor for hepatocellular carcinoma. Lifestyle and eating habit changes during the last century have made NAFLD the most common liver disease linked to obesity, type 2 diabetes mellitus and dyslipidemia, with a global prevalence of 25%. NAFLD arises when the uptake of fatty acids (FA) and triglycerides (TG) from circulation and de novo lipogenesis saturate the rate of FA \( \beta \)-oxidation and very-low density lipoprotein (VLDL)-TG export. Deranged lipid metabolism is also associated with NAFLD progression from steatosis to NASH, and therefore, alterations in liver and serum lipidomic signatures are good indicators of the disease's development and progression. This review focuses on the importance of the classification of NAFLD patients into different subtypes, corresponding to the main alteration(s) in the major pathways that regulate FA homeostasis leading, in each case, to the initiation and progression of NASH. This concept also supports the targeted intervention as a key approach to maximize therapeutic efficacy and opens the door to the development of precise NASH treatments. The authors state that a challenge in NAFLD research is the identification of which patients with NAFLD will develop NASH and, for those with NASH, how fast the disease will progress. At present, it is premature to conclude which of these blood biomarkers, alone or in combination, would be best to precisely and rapidly diagnose the severity of NASH and monitor the liver's response to treatment.

In their review, Zhou et al (2019) state with the increasing number of individuals with diabetes and obesity, nonalcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent, affecting one-quarter of adults worldwide. The spectrum of NAFLD ranges from simple steatosis or nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH). NAFLD, especially NASH, may progress to fibrosis, leading to cirrhosis and hepatocellular carcinoma. NAFLD can impose a severe economic burden, and patients with NAFLD-related terminal or deteriorative liver diseases have become one of the main
groups receiving liver transplantation. The increasing prevalence of NAFLD and the severe outcomes of NASH make it necessary to use effective methods to identify NAFLD. Although recognized as the gold standard, biopsy is limited by its sampling bias, poor acceptability, and severe complications, such as mortality, bleeding, and pain. Therefore, noninvasive methods are urgently needed to avoid biopsy for diagnosing NAFLD. This review discusses the current noninvasive methods for assessing NAFLD, including steatosis, NASH, and NAFLD-related fibrosis, and explores the advantages and disadvantages of measurement tools. In addition, the authors analyze potential noninvasive biomarkers for tracking disease processes and monitoring treatment effects, and explore effective algorithms consisting of imaging and nonimaging biomarkers for diagnosing advanced fibrosis and reducing unnecessary biopsies in clinical practice. The authors state there are currently no effective noninvasive biomarkers recommended for diagnosing NASH. Future studies are needed to investigate more efficient noninvasive biomarkers for distinguishing NASH from simple steatosis.

Furthermore, an UpToDate review on “Tests used for the noninvasive assessment of hepatic fibrosis” (Curry and Afdhal, 2013) states that “While tremendous progress has been made in improving the accuracy of serum markers of hepatic fibrosis, they cannot yet supplant direct analysis of the liver. The ideal fibrosis marker is one that is specific, biologically based, noninvasive, easily repeated in all patients, correlates well with disease severity and outcome, and is not confounded by co-morbidities or drugs. Although this ideal has nearly been reached, no serum test has emerged as the perfect marker of fibrosis; all the serum tests have limitations …. Overall, the serum assay approaches remain promising, in part because these tests may represent an integrated readout of liver activity, rather than a minute sampling of the type obtained by conventional liver biopsy”.

Proprietary
In a UpToDate review "Noninvasive assessment of hepatic fibrosis: Overview of serologic and radiographic tests", (Curry and Afdhal, 2019), the authors state that noninvasive tests of hepatic fibrosis have been used in many clinical scenarios. The majority of studies of serologic markers and radiologic tests have looked at the use of these tests for staging of fibrosis in patients with chronic liver disease. The authors typically consider noninvasive testing for patients presenting for evaluation of chronic viral hepatitis. However, all the serum tests have limitations, such as they typically reflect the rate of matrix turnover, not deposition, and thus tend to be more elevated when there is high inflammatory activity. By contrast, extensive matrix deposition can go undetected if there is minimal inflammation. Also, none of the markers are liver-specific, and concurrent sites of inflammation or fibrosis may contribute to serum levels. Serum levels are affected by clearance rates, which may be impaired either due to sinusoidal endothelial cell dysfunction or impaired biliary excretion. Lastly, serum tests are surrogates, not biomarkers.

Houot et al (2016) selected studies from 2002 to 2014 that directly compared the diagnostic accuracy of FibroTest, aspartate aminotransferase-platelet ratio index (APRI), FIB4 index or transient elastography (TE), with biopsy as a reference, in patients with CHC or chronic hepatitis B (CHB). Investigators abstracted and checked study details and quality by using pre-defined criteria. Bayesian method in intention to diagnose was the primary outcome. Of 1321 articles identified, 71 studies including 77 groups according to etiology (All-CB) were eligible: 37 Only-C, 28 Only-B and 12 Mixed-C-B. There were 185 direct comparisons between the area under the ROC curves (AUROCs), 99 for the diagnosis of advanced fibrosis and 86 for cirrhosis. In All-CB, Bayesian analyses revealed significant AUROCs differences in identifying advanced fibrosis in favor of FibroTest vs. TE [credibility interval: 0.06 (0.02-0.09)], FibroTest vs. APRI [0.05 (0.03-0.07)] and for identifying cirrhosis TE vs. APRI [0.07 (0.02-0.13)] and FIB4 vs. APRI [0.04(0.02-0.05)]. No differences were observed.
between TE and FibroTest, for identifying cirrhosis in All-CB, and in sub-groups (Only-C, Only-B, Mixed-CB) for both cirrhosis and fibrosis. The investigators concluded that in CHC and CHB, APRI had lower performances than FIB-4, TE and FibroTest. TE had lower performance than FibroTest for identifying advanced fibrosis in All-CB, without significant difference for identifying cirrhosis in all groups.

Neuman et al (2016) noted that chronic liver diseases may cause inflammation and progressive scarring, over time leading to irreversible hepatic damage (cirrhosis). As a result, the need to assess and closely monitor individuals for risk factors of components of matrix deposition and degradation, as well as the severity of the fibrosis using biomarkers, has been increasingly recognized. These investigators reviewed the use of biomarker for diagnosing and defining the severity of liver fibrosis. A systematic literature review was performed using the terms "hyaluronic acid" and "liver fibrosis" as well as the name of each biomarker or algorithm known to be employed. PubMed and Google Scholar were searched, and English language articles indexed between January 2010 and October 2014 in which HA was used as a marker of liver fibrosis were retrieved, regardless of the underlying liver disease. Each author read the publications separately and the results were analyzed and discussed. Biomarkers offer a potential prognostic or diagnostic indicator for disease manifestation, progression, or both. Serum biomarkers, including HA, have been used for many years. Emerging biomarkers such as metalloproteinases have been proposed as tools that provide valuable complementary information to that obtained from traditional biomarkers. Moreover, markers of extracellular matrix degradation provide powerful predictions of risk. In order for biomarkers to be clinically useful in accurately diagnosing and treating disorders, age-specific reference intervals that account for differences in gender and ethnic origin are a necessity.
World Health Organization guidelines on hepatitis B (WHO, 2015) state that "aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g., FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint. (Conditional recommendation, low quality of evidence)."

Guidelines on hepatitis C from the American Association for the Study of Liver Disease (AASLD) (Terrault, et al., 2015) state that "[e]valuation for stage of disease using noninvasive methods or liver biopsy is useful in guiding treatment decisions including duration of therapy." The guidelines explain that: "Serum markers of fibrosis, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4, FibroTest, and vibration-controlled transient elastography, have only moderate accuracy in identifying persons with significant fibrosis (fibrosis stage 2 or greater on the Metavir scale), but good diagnostic accuracy in excluding advanced fibrosis and may be useful aids in decision making."

The 2019 hepatitis C guidance update from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (Ghany 2020) state assessing liver disease severity is an essential component of the workup for all persons with newly diagnosed chronic hepatitis C as this factor influences initial and follow-up evaluation. This assessment (i.e., presence or absence of cirrhosis) can usually be accomplished with noninvasive tests. Liver biopsy is rarely required but is a consideration if other causes of liver disease are suspected. Noninvasive tests to assess liver Disease Severity include: liver-directed physical exam (normal in most patients); routine blood tests (e.g., ALT, AST, albumin, bilirubin, INR, and CBC with platelet count); serum fibrosis marker panels; transient
elastography, liver imaging (e.g., ultrasound or computed tomography scan); AST-to-platelet ratio index; and FIB-4 score.

The guidance further states that the simplified HCV treatment algorithm for adults without cirrhosis who have not been previously treated for their infection and do not have evidence of cirrhosis as defined by the noninvasive parameters specified in the HCV guidance. The guidance further describes evidence of cirrhosis as a FIB-4 score > 3.25, or any of the following findings from a previously performed test: transient elastography indicating cirrhosis (e.g., FibroScan [Echosens, Paris, France] stiffness more than 12.5 kPa), noninvasive serologic tests that exceed proprietary cutoffs (e.g., FibroSure [BioPredictive, Paris, France], Enhanced Liver Fibrosis Test [Siemens Healthcare, Erlangen, Germany], etc.), clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count < 150,000/mm3, etc.), and/or prior liver biopsy showing cirrhosis.

Castiella et al (2010) stated that advances in recent years in the understanding of, and the genetic diagnosis of hereditary hemochromatosis (HH) have changed the approach to iron overload hereditary diseases. The ability to use a radiologic tool (MRI) that accurately provides liver iron concentration (LIC) determination, and the presence of non-invasive serologic markers for fibrosis prediction (serum ferritin, platelet count, transaminases, etc.), have diminished the need for liver biopsy for diagnosis and prognosis of this disease. Consequently, the role of liver biopsy in iron metabolism disorders is changing. Furthermore, the irruption of transient elastography to assess liver stiffness, and, more recently, the ability to determine liver fibrosis by means of MRI elastography will change this role even more, with a potential drastic decline in hepatic biopsies in years to come. These investigators provided a brief summary of the different non-invasive methods available nowadays for diagnosis and prognosis in HH, and pointed out potential new techniques that could come
about in the next years for fibrosis prediction, thus avoiding the need for liver biopsy in a greater number of patients. It is possible that liver biopsy will remain useful for the diagnosis of associated diseases, where other non-invasive means are not possible, or for those rare cases displaying discrepancies between radiological and biochemical markers. The authors concluded that based on the advances during the last few years, biochemical markers, LIC determination by MRI (Fibrosis index) and FibroScan and, probably, MR elastography, all constitute reliable non-invasive means for detecting liver fibrosis. The role of liver biopsy in the study of hemochromatosis is decreasing. In future, it appeared that liver biopsy will only be performed for diagnosis of associated diseases, or in patients where discrepancies between radiologic and biochemical markers exist. These investigators believed it is time to take a step forward and to reduce the “faith” in liver biopsy in favor of non-invasive methods for liver fibrosis prediction.

Also, an UpToDate review on “Clinical manifestations and diagnosis of hereditary hemochromatosis” (Schrier and Bacon, 2018) states that “with the availability of ultrasound-based elastography as a test for detecting advanced hepatic fibrosis, it is even less likely that the liver biopsy would be performed in those with HH. These non-invasive ways of detecting fibrosis to identify patients who are candidates for screening for varices and liver cell cancers seem much more reasonable than a liver biopsy”.

Enhanced Liver Fibrosis (ELF) Test

The Enhanced Liver Fibrosis Test by Siemens Healthcare is a blood based analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], and tissue inhibitor of metalloproteinase 1 [TIMP-1]). Sherman et al (2020) state noninvasive fibrosis markers are routinely used in patients with liver disease. Magnetic resonance elastography (MRE) is recognized as a highly accurate methodology, but a
reliable blood test for fibrosis would be useful. The authors examined performance characteristics of the Enhanced Liver Fibrosis (ELF) Index compared to MRE in a cohort including those with HCV, HIV, and HCV/HIV. Subjects enrolled in the Miami Adult Studies on HIV (MASH) cohort underwent MRE and blood sampling. The ELF Index was scored and receiver-operator curves constructed to determine optimal cutoff levels relative to performance characteristics. Cytokine testing was performed to identify new markers to enhance noninvasive marker development. The ELF Index was determined in 459 subjects; more than half were male, non-white, and HIV-infected. MRE was obtained on a subset of 283 subjects and the group that had both studies served as the basis of the receiver-operator curve analysis. At an ELF Index of > 10.633, the area under the curve for cirrhosis (Metavir F4, MRE > 4.62 kPa) was 0.986 (95% CI 0.994-0.996; p < 0.001) with a specificity of 100%. For advanced fibrosis (Metavir F3/4), an ELF cutoff of 10 was associated with poor sensitivity but high specificity (98.9%, 95% CI 96.7-99.8%) with an AUC of 0.80 (95% CI 0.749-0.845). ELF Index performance characteristics exceeded FIB-4 performance. HCV and age were associated with increased fibrosis (p < 0.05) in a multivariable model. IP-10 was found to be a promising biomarker for improvement in noninvasive prediction algorithms. The authors concluded that the ELF Index was a highly sensitive and specific marker of cirrhosis, even among HIV-infected individuals, when compared with MRE. IP-10 may be a biomarker that can enhance performance characteristics further, but additional validation is required.

Inadomi et al (2020) state the Enhanced Liver Fibrosis (ELF) test comprises a logarithmic algorithm combining three serum markers of hepatic extracellular matrix metabolism. The authors aimed to evaluate the performance of ELF for the diagnosis of liver fibrosis and to compare it with that of liver stiffness measurement (LSM) by FibroScan in non-alcoholic fatty liver disease (NAFLD). ELF cut-off values for the diagnosis of advanced fibrosis were obtained using receiver
operating characteristic (ROC) analysis in patients with biopsy-confirmed NAFLD (training set; n=200). Diagnostic performance was analyzed in the training set and in a validation set (n=166), and compared with that of LSM in the FibroScan cohort (n=224). The area under ROC curve was 0.81 for the diagnosis of advanced fibrosis and the ELF cut-off values were 9.34 with 90.4% sensitivity and 10.83 with 90.6% specificity in the training set, and 89.8% sensitivity and 85.5% specificity in the validation set. There was no significant difference in the area under the ROC curve between ELF and LSM (0.812 and 0.839). A combination of ELF (cut-off 10.83) and LSM (cut-off 11.45) increased the specificity to 97.9% and the positive predictive value, versus ELF alone. Sequential use of the fibrosis-4 index (cut-off 2.67) and ELF (cut-off 9.34) increased the sensitivity to 95.9%. ELF can identify advanced liver fibrosis in NAFLD and its diagnostic accuracy is comparable to that of FibroScan. According to the clinical setting, combinations or sequential procedures using other non-invasive tests complement the diagnostic performance of ELF for the identification of advanced fibrosis.

The July 2016 National Institute for Health and Care Excellence (NICE) guidance for the assessment for advanced liver fibrosis in people with non-alcoholic fatty liver disease (NAFLD) recommends considering using the enhanced liver fibrosis (ELF) test in people who have been diagnosed with NAFLD to test for advanced liver fibrosis (Glen 2016).

Micro-Fibrillar Associated Glycoprotein 4 (MFAP4)

Molleken et al (2016) noted that several comparable mechanisms have been identified for hepatic and pulmonary fibrosis. The human micro-fibrillar associated glycoprotein 4 (MFAP4), produced by activated myofibroblasts, is a ubiquitous protein playing a potential role in extra-cellular matrix (ECM) turnover and was recently identified as biomarker for hepatic fibrosis in hepatitis C patients. These researchers evaluated serum levels of MFAP4 in patients with
pulmonary fibrosis in order to test its potential as biomarker in clinical practice. They also examined if MFAP4 deficiency in mice affects the formation of pulmonary fibrosis in the bleomycin model of lung fibrosis. A total of 91 patients with idiopathic pulmonary fibrosis (IPF), 23 with hypersensitivity pneumonitis (HP) and 31 healthy subjects were studied. In the mouse model, C57BL/6 Mfap4+/+ and Mfap4-/- mice between 6 to 8 weeks of age were studied. Serum levels of MFAP4 were measured by ELISA in patients and in mice. Surfactant protein D (SP-D) and LDH were measured as comparison biomarkers in patients with pulmonary fibrosis. Morphometric assessment and the Sircol kit were used to determine the amount of collagen in the lung tissue in the mouse model. Serum levels of MFAP4 were not elevated in lung fibrosis -- neither in the patients with IPF or HP nor in the animal model. Furthermore no significant correlations with pulmonary function tests of IPF patients could be found for MFAP4; MFAP4 levels were increased in BAL of bleomycin-treated mice with pulmonary fibrosis. The authors concluded that MFAP4 is not elevated in sera of patients with pulmonary fibrosis or bleomycin-treated mice with pulmonary fibrosis. This may be due to different pathogenic mechanisms of liver and lung fibrogenesis. They stated that MFAP4 appeared to be useful as serum biomarker for hepatic but not for lung fibrosis. These preliminary findings need to be validated by well-designed studies.

MicroRNA-21

Zhao and colleagues (2014) stated that microRNA-21 (miR-21) plays an important role in the pathogenesis and progression of liver fibrosis. These researchers determined the serum and hepatic content of miR-21 in patients with liver cirrhosis and rats with dimethylnitrosamine-induced hepatic cirrhosis and examined the effects of miR-21 on SPRY2 and HNF4α in modulating ERK1 signaling in hepatic stellate cells (HSCs) and epithelial-mesenchymal transition (EMT) of hepatocytes. Quantitative real-time polymerase chain reaction (RT-PCR)
was used to determine miR-21 and the expression of SPRY2, HNF4α and other genes. Immunoblotting assay was performed to examine the expression of relevant proteins. Luciferase reporter assay was performed to assess the effects of miR-21 on its predicted target genes SPRY2 and HNF4α. Primary HSCs and hepatocytes were treated with miR-21 mimics/inhibitors or appropriate adenoviral vectors to examine the relation between miR-21 and SPRY2 or HNF4α. The serum and hepatic content of miR-21 was significantly higher in cirrhotic patients and rats. SPRY2 and HNF4α mRNA levels were markedly lower in the cirrhotic liver. MiR-21 overexpression was associated with enhanced ERK1 signaling and EMT in liver fibrosis. Luciferase assay revealed suppressed SPRY2 and HNF4α expression by miR-21. Ectopic miR-21 stimulated ERK1 signaling in HSCs and induced hepatocyte EMT by targeting SPRY2 or HNF4α. Down-regulating miR-21 suppressed ERK1 signaling, inhibited HSC activation, and blocked EMT in TGFβ1-treated hepatocytes. The authors concluded that MiR-21 modulated ERK1 signaling and EMT in liver fibrosis by regulating SPRY2 and HNF4α expression; MiR-21 may serve as a potentially biomarker as well as intervention target for hepatic cirrhosis.

Kitano and Bloomston (2016) noted that miRNAs are small non-coding RNAs that regulate gene expression by either blocking translation or inducing degradation of target mRNA. Hepatic stellate cells play a central role in development of hepatic fibrosis and there are intricate regulatory effects of miRNAs on their activation, proliferation, collagen production, migration, and apoptosis. There are multiple differentially expressed miRNAs in activated HSCs, and these researchers summarized current data on miRNAs that participate in the development of hepatic fibrosis. The authors concluded that miRNAs may serve as biomarkers for diagnosis of liver disease, as well as markers of disease progression. Most importantly, dysregulated miRNAs may potentially be targeted by novel therapies to treat and reverse progression of hepatic fibrosis.
Signal-Induced Proliferation-Associated 1 Like 1 (SIPA1L1)

Marfa et al (2016) noted that currently several procedures are used for staging liver fibrosis. However, these methods may involve clinical complications and/or present diagnostic uncertainty mainly in the early stages of the disease. This study was designed to unveil new non-invasive biomarkers of liver fibrosis in an in-vivo model of fibrosis/cirrhosis induction by CCl4 inhalation by using a label-free quantitative LC-MS/MS approach. These researchers analyzed 94 serum samples from adult Wistar rats with different degrees of liver fibrosis and 36 control rats. Firstly, serum samples from 18 CCl4-treated rats were clustered into 3 different groups according to the severity of hepatic and the serum proteome was characterized by label-free LC-MS/MS. Furthermore, 3 different pooled serum samples obtained from 16 control Wistar rats were also analyzed. Based on the proteomic data obtained, these investigators performed a multivariate analysis that displayed 3 main cell signaling pathways altered in fibrosis. In cirrhosis, more biological imbalances were detected as well as multi-organ alterations. In addition, hemopexin and signal-induced proliferation-associated 1 like 1 (SIPA1L1) were selected as potential serum markers of liver fibrogenesis among all the analyzed proteins. The results were validated by ELISA in an independent group of 76 fibrotic/cirrhotic rats and 20 controls that confirmed SIPA1L1 as a potential non-invasive biomarker of liver fibrosis. In particular, SIPA1L1 showed a clear diminution in serum samples from fibrotic/cirrhotic rats and a great accuracy at identifying early fibrotic stages. The authors concluded that the proteomic analysis of serum samples from CCl4-treated rats has enabled the identification of SIPA1L1 as a non-invasive marker of early liver fibrosis. These preliminary findings of an in-vivo study need to be validated by well-designed studies in human subjects.

Transient Elastography
Ultrasound transient elastography (eg, FibroScan) is a noninvasive, bedside ultrasonic technique to evaluate liver fibrosis by measuring liver stiffness. Transient elastography is based on the theory that fibrosis makes the liver stiffer and that elastic waves move more quickly through stiff tissue than through normal tissue. The device consists of a control unit (computer-based), a low-frequency (50 Hz) vibration emitter and a high-frequency (5 MHz) ultrasound probe. When the vibration emitter is pressed between the ribs on the right side of the body, a low-frequency elastic sheer wave is propagated through the liver. The stiffness is proportional to the square of the velocity of the shear wave, which is measured in kilopascals (kPa). There are approximately five to 10 readings taken and the median is used as the final value. In cirrhotic patients, liver stiffness measurements range from 12.5 to 75.5 kPa (kPa).

In a prospective study, de Ledinghen et al (2006) evaluated the accuracy of liver stiffness measurement for the detection of fibrosis and cirrhosis in HIV/hepatitis C virus (HCV)-coinfected patients and compared its accuracy with other non-invasive methods. These researchers studied 72 consecutive HIV patients with chronic hepatitis C who had a simultaneous liver biopsy and liver stiffness measurement by transient elastography (FibroScan; Echosens, Paris, France) for the assessment of liver fibrosis. Liver stiffness values ranged from 3.0 to 46.4 kPa. Liver stiffness was significantly correlated to fibrosis stage (Kendall tau-β = 0.48; p < 0.0001). The area under the receiver operating characteristic (AUROC) curve of liver stiffness measurement was 0.72 for F > or = 2 and 0.97 for F = 4. For the diagnosis of cirrhosis, AUROC curves of liver stiffness measurement were significantly higher than those for platelet count (p = 0.02), aspartate aminotransferase/ALT ratio (p = 0.0001), Aspartate aminotransferase-to-Platelet Ratio Index (p = 0.01), and FIB-4 (p = 0.004). The authors concluded that liver stiffness measurement is a promising noninvasive method for the
assessment of fibrosis in HIV-infected patients with chronic HCV infection. They also noted that its use for the follow-up of these patients should be further evaluated.

Foucher and colleagues (2006) assessed the accuracy of FibroScan for the detection of cirrhosis in patients with chronic liver disease. A total of 711 patients with chronic liver disease were studied. Etiologies of chronic liver diseases were hepatitis C virus or hepatitis B virus infection, alcohol, non-alcoholic steatohepatitis, other, or a combination of the above etiologies. Liver fibrosis was evaluated according to the METAVIR score. Stiffness was significantly correlated with fibrosis stage ($r = 0.73, p < 0.0001$). Areas under the receiver operating characteristic curve (95% CI) were 0.80 (0.75 to 0.84) for patients with significant fibrosis ($F > 2$), 0.90 (0.86 to 0.93) for patients with severe fibrosis ($F3$), and 0.96 (0.94 to 0.98) for patients with cirrhosis. Using a cut off value of 17.6 kPa, patients with cirrhosis were detected with a positive predictive value and a NPV of 90%. Liver stiffness was significantly correlated with clinical, biological, and morphological parameters of liver disease. With an NPV greater than 90%, the cut off values for the presence of esophageal varices stage 2/3, cirrhosis Child-Pugh B or C, past history of ascites, hepatocellular carcinoma, and esophageal bleeding were 27.5, 37.5, 49.1, 53.7, and 62.7 kPa, respectively. The authors concluded that FibroScan is a promising non-invasive method for detection of cirrhosis in patients with chronic liver disease. They noted that its use for the follow-up and management of these patients could be of great interest and should be evaluated further.

Corpechot and associates (2006) assessed the diagnostic performance of liver stiffness measurement (LSM) for the determination of fibrosis stage in chronic cholestatic diseases. A total of 101 patients with primary biliary cirrhosis (PBC, $n = 73$) or primary sclerosing cholangitis (PSC, $n = 28$) were prospectively enrolled in a multi-center study. All patients underwent liver biopsy (LB) and LSM. Histological and fibrosis
stages were assessed on LB by two pathologists. LSM was performed by FibroScan. Efficiency of LSM for the determination of histological and fibrosis stages were determined by a ROC curve analysis. Analysis failed in 6 patients (5.9%) because of unsuitable LB (n = 4) or LSM (n = 2). Stiffness values ranged from 2.8 to 69.1 kPa (median of 7.8 kPa). LSM was correlated to both fibrosis (Spearman’s rho = 0.84, p < .0001) and histological (0.79, p < .0001) stages. These correlations were still found when PBC and PSC patients were analyzed separately. Areas under ROC curves were 0.92 for fibrosis stage (F) > or = 2, 0.95 for F > or = 3 and 0.96 for F = 4. Optimal stiffness cutoff values of 7.3, 9.8, and 17.3 kPa showed F > or = 2, F > or = 3 and F = 4, respectively. LSM and serum hyaluronic acid level were independent parameters associated with extensive fibrosis on LB. The authors concluded that FibroScan is a simple and reliable non-invasive means for assessing biliary fibrosis. They stated that it should be a promising tool to assess anti-fibrotic therapies in PBC or PSC.

The Canadian Agency for Drugs and Technologies in Health (CADTH) performed an evaluation on FibroScan for non-invasive assessment of liver fibrosis (Murtagh and Foster, 2006). It stated that the diagnostic performance of FibroScan is good for identifying severe fibrosis or cirrhosis, but it is less accurate for milder presentations. It concluded that FibroScan is a promising technology, but large multi-center studies comparing a range of emerging non-invasive fibrosis staging technologies are needed. An earlier assessment by the French Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT, 2004) reached similar conclusions, stating that the absence of conclusive evidence concerning the diagnostic value of FibroScan argues against its immediate dissemination. More recently, an assessment by the French National Authority for Health (HAS, 2007) concluded that additional studies are necessary to evaluate the comparative cost-effectiveness of different methods of assessing liver fibrosis (e.g., FibroTest, FibroScan, and biopsy).
assessment by the Malasian Ministry of Health (Darus, 2008) reached similar conclusions about the need for additional research for the Fibroscan.

de Franchis et al (2007) stated that transient elastography (Fibroscan) might be of value for the non-invasive diagnosis of cirrhosis; however, its reproducibility needs to be further validated. Furthermore, Berrutti et al (2007) noted that FibroScan is a new, non-invasive method to evaluate liver stiffness and, consequently, the degree of liver fibrosis. Since its use in the clinical setting is of great interest, further studies should define the exact role of this procedure.

de Lédinghen et al (2007) assessed the feasibility of liver stiffness measurement and compared FibroScan, FibroTest, and APRI with liver biopsy for the diagnosis of cirrhosis in children with chronic liver diseases. A total of 116 consecutive children with chronic liver diseases were prospectively included. All except 1 child (58 boys, mean age of 10.7 years) could have non-invasive tests for fibrosis: FibroScan, FibroTest, and APRI, and, when necessary, a liver biopsy (n = 33). FibroScan, FibroTest, and APRI were correlated with clinical or biological parameters of chronic liver diseases, but the FibroScan marker correlated most with all parameters. By histology, the METAVIR fibrosis category score was F1 in 7 cases, F2 in 8 cases, F3 in 6 cases, and F4 in 12 cases. FibroScan, FibroTest, and APRI were significantly correlated with the METAVIR fibrosis score. For the diagnosis of cirrhosis, AUC was 0.88, 0.73, and 0.73 for FibroScan, FibroTest, and APRI, respectively. The authors concluded that these findings indicated that liver stiffness measurement is feasible in children and is related to liver fibrosis. A specific probe dedicated to children and slender patients has thus been developed and is currently under evaluation. The FibroScan equipped with this specific probe could become a useful tool for the management of chronic liver diseases in children.
Shaheen et al (2007) stated that the accurate diagnosis of HCV-related fibrosis is crucial for prognostication and treatment decisions. Due to the limitations of biopsy, non-invasive alternatives including FibroTest and FibroScan have been developed. These investigators systematically reviewed studies describing the accuracy of these tests for predicting HCV-related fibrosis. Studies comparing FibroTest or FibroScan versus biopsy in HCV patients were identified via an electronic search. Random effects meta-analyses and AUC were examined to characterize test accuracy for significant fibrosis (F2 to F4) and cirrhosis. Heterogeneity was explored using meta-regression. A total of 12 studies were identified; 9 for FibroTest (n = 1,679) and 4 for FibroScan (n = 546). In heterogeneous analyses for significant fibrosis, the AUCs for FibroTest and FibroScan were 0.81 (95% confidence interval [CI] 0.78 to 0.84) and 0.83 (0.03 to 1.00), respectively. At a threshold of approximately 0.60, the sensitivity and specificity of the FibroTest were 47% (35% to 59%) and 90% (87% to 92%). For FibroScan (threshold approximately 8 kPa), corresponding values were 64% (50% to 76%) and 87% (80% to 91%), respectively.

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 FibroTest and FibroScan were 0.90 (95% CI not calculable) and 0.95 (0.87 to 0.99), respectively. The authors concluded that FibroTest and FibroScan have excellent utility for the identification of HCV-related cirrhosis, but lesser accuracy for earlier stages. They noted that refinements are necessary before these tests can replace liver biopsy.

Sagir et al (2008) noted that transient elastography (also known as FibroScan) is a rapid, non-invasive, and reproducible method for measuring liver stiffness, which correlates with the degree of liver fibrosis in patients with
chronic hepatitis. However, whether FibroScan is useful in the detection of pre-existing liver fibrosis/cirrhosis in patients presenting with acute liver damage is unclear. In this study, patients with acute liver damage of different etiologies were analyzed. Liver stiffness was measured during the acute phase of the liver damage and followed-up to the end of the acute phase. A total of 20 patients were included in the study. In 15 of the 20 patients, initial liver stiffness values measured by FibroScan during the acute phase of the liver damage were suggestive of liver cirrhosis. However, none of these 15 patients showed any signs of liver cirrhosis in the physical examination, ultrasound examination, or liver histology [performed in 11 of 15 (73%) patients]. A significant difference was observed in the initial bilirubin levels (5.8 +/- 6.5 mg/dL versus 15.7 +/- 11.8 mg/dL; p = 0.042) and age (32.4 +/- 17.5 years versus 49.7 +/- 15.8 years; p = 0.042) between patients with liver stiffness below or above 12.5 kPa. Six patients with initially high liver stiffness were followed-up to abatement of the acute hepatic phase; in all of them, liver stiffness values decreased to values below the cut-off value for liver cirrhosis. The authors concluded that transient elastography frequently yields pathologically high values in patients with acute liver damage and is unsuitable for detecting cirrhosis/fibrosis in these patients.

Han and Yoon (2008) stated that although liver biopsy is still the gold standard for assessing hepatic fibrosis, it has some technical limitations and risks. Furthermore, the dynamic process of liver fibrosis resulting from progression and regression can not be quantified by liver biopsy. Thus, alternative, simple, reliable and non-invasive tests are needed to assess the stage of fibrosis. Several non-invasive direct and indirect serum markers able to predict the presence of significant fibrosis or cirrhosis in patients with chronic liver disease with considerable accuracy have been reported. However, since most of these markers require complicated calculations, clinical application is difficult. Transient elastography (FibroScan) is a new method for the evaluation
of liver stiffness. It is based on changes in tissue elasticity induced by hepatic fibrosis. The authors noted that based on accumulating clinical data, clinical applications of elastography will increase in the near future.

Sporea and colleagues (2008) stated that evaluation of liver fibrosis can be performed by FibroTest, elastography (FibroScan), and by LB, which is considered to be the "gold standard". At the present, there are 3 techniques for performing LB: percutaneous, transjugular, and laparoscopic. The percutaneous LB can be performed blind, ultrasound (US)-guided or US-assisted. There are two main categories of specialists who perform LB: gastroenterologists (hepatologists) and radiologists, and the specialty of the individual who performs the LB determines if the LB is performed under ultrasound guidance or not. There are 2 types of biopsy needles used for LB: cutting needles (Tru-Cut, Vim-Silverman) and suction needles (Menghini, Klatzkin, Jamshidi). The rate of major complications after percutaneous LB ranges from 0.09% to 2.3%, but the echo-guided percutaneous liver biopsy is a safe method for the diagnosis of chronic diffuse hepatitis (cost-effective as compared to blind biopsy) and the rate of complications seems to be related to the experience of the physician and the type of the needle used (Menghini type needle seems to be safer). The authors stated that maybe in a few years non-invasive markers of fibrosis will be used, but at this time, most authorities in the field consider LB to be useful and necessary for the evaluation of chronic hepatopathies, despite the fact that it is not a perfect test.

Castera and associates (2008) stated that transient elastography (TE, FibroScan) is a novel non-invasive method that has been proposed for the assessment of hepatic fibrosis in patients with chronic liver diseases, by measuring liver stiffness. It is a rapid and user-friendly technique that can be easily performed at the bedside or in the outpatient clinic with immediate results and good reproducibility. Limitations include failure in approximately 5% of cases, mainly in obese
patients. So far, TE has been mostly validated in chronic hepatitis C, with diagnostic performance equivalent to that of serum markers for the diagnosis of significant fibrosis.
Combining TE with serum markers increases diagnostic accuracy and as a result, LB could be avoided for initial assessment in most patients with chronic hepatitis C. These investigators stated that this strategy warrants further evaluation in other etiological types of chronic liver diseases. Transient elastography appears to be an excellent tool for early detection of cirrhosis and may have prognostic value in this setting. As TE has excellent patient acceptance it could be useful for monitoring fibrosis progression and regression in the individual case, but more data are awaited for this application. Guidelines are needed for the use of TE in clinical practice.

In a meta-analysis, Friedrich-Rust et al (2008) examined the performance of TE for the staging of liver fibrosis. Literature data bases and international conference abstracts were searched. Inclusion criteria were as follows: evaluation of TE, LB as reference, and assessment of the area under the receiver operating characteristic curve (AUROC). The meta-analysis was performed using the random-effects model for the AUROC, summary receiver operating curve techniques, as well as meta-regression approaches. A total of 50 studies were included in the analysis. The mean AUROC for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were 0.84 (95 % CI: 0.82 to 0.86), 0.89 (95 % CI: 0.88 to 0.91), and 0.94 (95 % CI: 0.93 to 0.95), respectively. For the diagnosis of significant fibrosis a significant reduction of heterogeneity of the AUROC was found when differentiating between the underlying liver diseases (p < 0.001). Other factors influencing the AUROC were the scoring system used and the country in which the study was performed. Age, body mass index, and biopsy quality did not have a significant effect on the AUROC. The authors concluded that TE can be performed with excellent diagnostic accuracy and independent of the underlying liver disease for the diagnosis of cirrhosis.
However, for the diagnosis of significant fibrosis, a high variation of the AUROC was found that is dependent on the underlying liver disease. A critique of this meta-analysis by the Centre for Reviews and Dissemination (CRD, 2010) stated that, although sensitivity and specificity data appeared to have been available for many of the studies included in this meta-analysis, the meta-analysis focused on pooled estimates of AUROC. The CRD noted that use of this measure of overall accuracy results in a loss of clinically important information about test performance; it was unclear how many inaccurate test results were due to false positive and how many to false negatives. The CRD critique stated that generation of summary receiver operating characteristic (SROC) curves using a bivariate of hierarchical model may have been more appropriate to this data set; the CRD noted that such models allow generation of summary estimates of sensitivity and specificity as well as potential to assess the significance of sources of heterogeneity. The CRD concluded that these limitations in the analysis mean that the conclusions of this meta-analysis should be interpreted with caution.

Abenavoli et al (2008) noted that in clinical practice there are currently 3 methods for the evaluation of liver fibrosis. First, LB is still considered as the "gold standard" method. Second, serological markers and their mathematical combination were suggested in the last years as an alternative to LB. Third, TE was proposed recently. This technique (TE) is based on the progression speed of an elastic shear wave within the liver. The authors concluded that currently, there are just a few studies capable of evaluating the effectiveness of TE in evaluating chronic liver diseases, mainly in patients infected with HCV. Its application must also be studied in the monitoring of patients suffering from chronic HCV infection and subjected to treatments that can modify their degree of liver fibrosis.
Muñoz et al (2009) evaluated the correlation between values of Fibroscan, liver biopsy, and clinical data among HCV-positive renal transplant patients. A total of 24 HCV/RNA-positive patients with a previous liver biopsy were selected to undergo Fibroscan (transient elastography) and a clinical evaluation of liver function. Fibroscan values were expressed in kilopascals (kPa). As 2 patients were eliminated due to obesity or ascites, these investigators analyzed 22 patients. Thirteen patients (59%) with fibrosis F0-F1 (METAVIR score) by biopsy and normal liver function showed a mean Fibroscan score of 5.2 kPa (range of 2.3 to 6.8 kPa). Three patients (13.6%) exhibited F2 by biopsy and normal liver function with a mean Fibroscan score of 8.2 kPa (range of 7.3 to 8.9 kPa). Three patients (13.6%) with F3 by biopsy and abnormal liver function showed a high mean Fibroscan score of 10.9 kPa (range of 10.5 to 11.6 kPa). The last 3 patients (13.6%) with F4 (cirrhosis) by biopsy and abnormal clinical data showed the highest mean Fibroscan value of 14.2 kPa (range of 8.9 to 18 kPa). The authors concluded that among renal transplant patients with HCV, the values of Fibroscan seem to correlate with the degree of fibrosis by biopsy and with clinical liver function. Thus, Fibroscan may be useful to follow patients with LD. However, these results should be analyzed with caution due to the small number of cases and retrospective nature of the study.

Andersen and colleagues (2009) stated that liver biopsy is considered the "golden standard" for assessment of hepatic fibrosis. However, the procedure has limitations because of inconvenience and rare but serious complications such as bleeding. Furthermore, sampling errors are frequent, and interobserver variability often poses problems. Recently, transient elastography has been developed to assess fibrosis. The device measures liver elasticity, which correlates well with the degree of fibrosis. Studies have shown that transient elastography is more accurate in diagnosing cirrhosis than minor-to-moderate fibrosis. Most of the studies have been conducted on patients with chronic hepatitis but a few studies...
have also covered fibrosis and cirrhosis due to other
etiologies, and they also demonstrated the high sensitivity and
specificity. The authors concluded that transient elastography
for assessment of fibrosis may turn out to be a valuable
diagnostic procedure and follow-up of patients with chronic
liver diseases.

Breton et al (2009) examined the feasibility and reliability of
liver stiffness measurement in children with liver diseases.
Liver stiffness measurements were performed on 72 children,
from 4 to 18 years of age, with potential hepatic fibrosis
disease. The clinical, biological, ultrasonographic, and
endoscopic parameters were noted to identify children with
portal hypertension syndrome. The APRI (ASAT-to-platelet
ratio index) test was calculated according to the standard
formula. An APRI test score higher than 1.5 indicates
significant hepatic fibrosis. METAVIR scoring from 14 liver
biopsies was compared to the liver stiffness using the Kappa
statistic. A total of 28 patients had viral hepatitis, 20 cystic
fibrosis, 16 chronic liver cholestasis, 5 autoimmune hepatitis,
and 3 patients had liver fibrosis with uncertain etiology.
FibroScan measurements were available in all children. There
was good agreement between FibroScan and pathological
studies (weighted kappa = 0.814). Only 9 children had portal
hypertension syndrome with an average measurement of liver
stiffness significantly higher than children without portal
hypertension (26.5kPa versus 6.4kPa; p < 0.01). The APRI
test for 6 out of 9 patients scored higher than 1.5. The authors
concluded that these findings indicate that liver stiffness
measurement is feasible in children and seems to be related to
liver fibrosis. They stated that larger prospective studies are
needed to validate this FibroScan method.

In a meta-analysis of transient elastography for the detection
of hepatic fibrosis, Stebbing et al (2010) evaluated its use in
comparison with liver biopsy. Studies from the literature were
analyzed with a median liver stiffness value in kilopascal given
for fibrosis stages according to histopathologic findings on
biopsy and best discriminant cut-off levels in kilopascals for significant fibrosis (greater than or equal to F2) and cirrhosis (F4). A total of 22 studies were selected comprising 4,430 patients; chronic hepatitis C infection was the most common etiology of fibrosis. The pooled estimates for significant fibrosis (greater than or equal to F2) measured 7.71 kPa (LSM cut-off value) with a sensitivity of 71.9 % [95 % CI: 71.4 % to 72.4 %] and specificity of 82.4 % (95 % CI: 81.9 % to 82.9 %), whereas for cirrhosis (F4) the results showed a cut-off of 15.08 kPa with a sensitivity of 84.45 % (95 % CI: 84.2 % to 84.7 %) and specificity of 94.69 % (95 % CI: 94.3 % to 95 %). The authors concluded that further evaluation of transient elastography to assess LSM is needed in prospective studies to potentially increase the sensitivity and establish its clinical utility.

Myers (2009) noted that non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, affecting about 30 % of Western populations and a frequent indication for liver transplantation. The histological spectrum of NAFLD includes simple steatosis, which has a benign prognosis, and non-alcoholic steatohepatitis, a more aggressive form of liver injury that may progress to cirrhosis and its complications. At present, the only widely accepted means of differentiating these lesions, including the severity of hepatic fibrosis, is liver biopsy. However, due to the invasiveness of this procedure, the rising prevalence of NAFLD, and the expected availability of effective therapies for this condition, the identification of non-invasive tools for the diagnosis and staging of NAFLD has emerged as a major clinical and research priority. The author summarized important advances in this field during the past decade, including the development of biomarkers of hepatic fibrosis, apoptosis, and inflammation; novel imaging techniques such as transient elastography; and high-throughput technologies including proteomics and genomics. Future studies must focus on the development of accurate, inexpensive, and reliable tools that can differentiate the major histologic
determinants of NAFLD; are responsive to changes in NAFLD severity due to therapeutic intervention and time; and have prognostic significance. Until such tools are developed, liver biopsy remains an important tool in the assessment of patients with NAFLD.

Myers and co-workers (2010) determined the feasibility and performance of TE in a North American cohort of patients with chronic liver disease. Liver stiffness measurements were obtained using TE in 260 patients with chronic hepatitis B or C, or NAFLD from 4 Canadian hepatology centers. The accuracy of TE compared with liver biopsy for the prediction of significant fibrosis (Metavir fibrosis score of F2 or greater), bridging fibrosis (Metavir fibrosis score of F3 or greater) and cirrhosis (Metavir fibrosis score of F4) was assessed using area under ROC curves (AUROCs), and compared with the aspartate aminotransferase-to-platelet ratio index. The influence of ALT levels and other factors on liver stiffness was determined using linear regression analyses. Failure of TE occurred in 2.7% of patients, while liver biopsies were inadequate for staging in 0.8%. Among the remaining 251 patients, the AUROCs of TE for Metavir fibrosis scores of F2 and F3 or greater, and F4 were 0.74 (95% CI: 0.68 to 0.80), 0.89 (95% CI: 0.84 to 0.94), and 0.94 (95% CI: 0.90 to 0.97), respectively. Liver stiffness measurement was more accurate than the aminotransferase-to-platelet ratio index for bridging fibrosis (AUROC 0.78) and cirrhosis (AUROC 0.88), but not significant fibrosis (AUROC 0.76). At a cut-off of 11.1 kPa, the sensitivity, specificity, and positive and negative predictive values for cirrhosis (prevalence 11%) were 96%, 81%, 39% and 99%, respectively. For significant fibrosis (prevalence 53%), a cut-off of 7.7 kPa was 68% sensitive and 69% specific, and had a positive predictive value of 70% and a negative predictive value of 65%. Liver stiffness was independently associated with ALT, body mass index and steatosis. The optimal LSM cut-offs for cirrhosis were 11.1 kPa and 11.5 kPa in patients with ALT levels lower than 100 U/L and 100 U/L or greater, respectively. For fibrosis scores of F2 or greater,
these figures were 7.0 kPa and 8.6 kPa, respectively. The authors concluded that the major role of TE is the exclusion of bridging fibrosis and cirrhosis. However, TE can not replace biopsy for the diagnosis of significant fibrosis. Because liver stiffness may be influenced by significant ALT elevation, body mass index and/or steatosis, tailored liver stiffness cut-offs may be necessary to account for these factors.

Cholongitas et al (2010) systematically reviewed the literature regarding non-invasive tests (NIT) following liver transplantation. These investigators identified 14 studies evaluating NIT based on serum markers and/or liver imaging techniques: 10 studies assessed NIT in recipients with recurrent HCV infection for fibrosis and 4 studies evaluated predictors of progression of fibrosis in recurrent HCV. Transient Elastography had good discrimination for significant fibrosis (median AUROC: 0.88). Among the serum NIT, APRI had good performance (median AUROC: 0.75). Transient elastography performed better than serum (direct and indirect) NIT for significant fibrosis with median AUROC 0.88 (versus 0.66, \( p < 0.001 \)), median sensitivity 0.86 (versus 0.56, \( p = 0.002 \)), median NPV 0.90 (versus 0.74, \( p = 0.05 \)) and median positive predictive value (PPV) 0.80 (versus 0.63, \( p = 0.02 \)). Transient elastography compared to indirect serum NIT, had better performance, but was not superior to APRI score. Finally, direct, compared to indirect NIT, were not significantly different except for specificity: median: 0.83 versus 0.69, respectively, \( p = 0.04 \). The authors concluded that NIT could become an important tool in clinical management of liver transplant recipients, but whether they can improve clinical practice needs further evidence. Their optimal combination with liver biopsy and assessment of collagen content requires investigation.

Stebing et al (2010) performed a meta-analysis to further assess the use of TE in comparison with liver biopsy. Studies from the literature were analyzed with a median liver stiffness value in kilopascal given for fibrosis stages according to
histopathologic findings on biopsy and best discriminant cutoff levels in kilopascals for significant fibrosis (greater than or equal to F2) and cirrhosis (F4). A total of 22 studies were selected comprising 4,430 patients; chronic hepatitis C infection was the most common etiology of fibrosis. The pooled estimates for significant fibrosis greater than or equal to F2) measured 7.71 kPa (LSM cut-off value) with a sensitivity of 71.9 % [95 % CI: 71.4 % to 72.4 %] and specificity of 82.4 % (95 % CI: 81.9 % to 82.9 %), whereas for cirrhosis (F4) the results showed a cut-off of 15.08 kPa with a sensitivity of 84.45 % (95 % CI: 84.2 % to 84.7 %) and specificity of 94.69 % (95 % CI: 94.3 % to 95 %). The authors concluded that further evaluation of TE to assess LSM is needed in prospective studies to potentially increase the sensitivity and establish its clinical utility.

Thabut et al (2011) noted that severe portal hypertension is responsible for complications and death. Although measurement of the hepatic venous pressure gradient is the most accurate method for evaluating the presence and severity of portal hypertension, this technique is considered invasive and is not routinely performed in all centers. Several non-invasive techniques have been proposed to measure portal hypertension. Certain methods evaluate elements related to the pathogenesis of portal hypertension through the measurement of hyperkinetic syndrome, or they examine the development of hepatic fibrosis through the measurement of increased intra-hepatic vascular resistance. Other methods assess the clinical consequences of portal hypertension, such as the presence of esophageal varices or the development of porto-systemic shunts. Methods evaluating increased hepatic vascular resistance are fairly accurate and primarily involve the detection of hepatic fibrosis by serum markers and transient elastography. The radiological assessment of hyperkinetic syndrome probably has value but is still under investigation. The assessment of severe portal hypertension by the presence of varices may be performed with simple tools such as biological assays,
computed tomography, and esophageal capsules. More sophisticated procedures seem promising but are still under development. Screening tools for large populations must be simple, whereas more complicated procedures could help in the follow-up of already diagnosed patients. Although most of these non-invasive methods effectively identify severe portal hypertension, methods for diagnosing moderate portal hypertension need to be developed; this shows that further investigation is needed in this field.

Tsochatzis et al (2011) studied the performance of elastography for diagnosis of fibrosis using meta-analysis. MEDLINE, EMBASE, SCI, Cochrane Library, conference abstracts books, and article references were searched. These investigators included studies using biopsy as a reference standard, with the data necessary to calculate the true- and false-positive, true- and false-negative diagnostic results of elastography for a fibrosis stage, and with a 3-month maximum interval between tests. The quality of the studies was rated with the QUADAS tool. These researchers identified 40 eligible studies. Summary sensitivity and specificity was 0.79 (95 % CI: 0.74 to 0.82) and 0.78 (95 % CI: 0.72 to 0.83) for F2 stage and 0.83 (95 % CI: 0.79 to 0.86) and 0.89 (95 % CI: 0.87 to 0.91) for cirrhosis. After an elastography result at/over the threshold value for F2 or cirrhosis ("positive" result), the corresponding post-test probability for their presence (if pre-test probability was 50 %) was 78 %, and 88 %, respectively, while, if values were below these thresholds ("negative" result), the post-test probability was 21 % and 16 %, respectively. No optimal stiffness cut-offs for individual fibrosis stages were validated in independent cohorts and cut-offs had a wide range and overlap within and between stages. The authors concluded that elastography theoretically has good sensitivity and specificity for cirrhosis (and less for lesser degrees of fibrosis); however, it should be cautiously applied to everyday clinical practice because there is no validation of the stiffness cut-offs for the various stages.
They stated that such validation is required before elastography is considered sufficiently accurate for non-invasive staging of fibrosis.

An UpToDate review on "Epidemiology, clinical features, and diagnosis of nonalcoholic steatohepatitis" (Sheth and Chopra, 2012) states that "A potentially useful non-invasive method for excluding advanced fibrosis is measurement of liver stiffness with transient elastography. However, the approach is not widely available and has not been extensively studied in NASH".

Poca et al (2011) stated that prognostic markers of compensated cirrhosis should mainly investigate factors involved with progression to decompensation because death in cirrhosis is related with decompensation. Portal hypertension plays a crucial role in the pathophysiology of most complications of cirrhosis. Accordingly, hepatic venous pressure gradient (HVPG) monitoring has strong prognostic value. An HVPG of greater than or equal to 10 mm Hg determines a significantly higher risk of developing decompensation. Esophageal varices also can develop when the HVPG is greater than or equal to 10 mm Hg, although an HVPG greater than or equal to 12 mm Hg is required for variceal bleeding to occur. Monitoring the changes induced by the treatment of portal hypertension on HVPG, provides strong prognostic information. In compensated cirrhosis hemodynamic response is appropriate when the HVPG decreased to less than 10 mm Hg or by less than 10 % from baseline, because the incidence of complications such as bleeding or ascites significantly decrease when these targets are achieved. Whether serum markers, such as the FibroTest, may be valuable to predict decompensation should be established. Transient elastography is a promising technique that has shown an excellent accuracy to detect severe portal hypertension. However, whether it can adequately determine
clinically significant portal hypertension, and risk of developing varices and decompensation, should be established. Magnetic resonance elastography is also promising.

Pesce and co-workers (2012) noted that portal hypertension has been reported as a negative prognostic factor and a relative contraindication for liver resection. These researchers considered a possible role of fibrosis evaluation by transient elastography (FibroScan) and its correlation with portal hypertension in patients with cirrhosis, and discussed the use of this technique in planning therapeutic options in patients with hepato-cellular carcinoma (HCC). A total of 77 patients with cirrhosis, 42 (54.5%) of whom had HCC, were enrolled in this study during 2009 to 2011. The group included 46 (59.7%) men. The mean age of the sample was 65.2 years. The principle etiology of disease was HCV-related cirrhosis (66.2%). Liver function was assessed according to Child-Pugh classification. In all patients liver stiffness (LS) was measured using FibroScan. The presence of portal hypertension was indirectly defined as: (i) esophageal varices detectable on endoscopy; (ii) splenomegaly (increased diameter of the spleen to greater than or equal to 12 cm), or (iii) a platelet count of less than 100,000 platelets/mm(3). Median LS in all patients was 27.9 kPa. Portal hypertension was recorded as present in 37 patients (48.1%) and absent in 40 patients (51.9%). Median LS values in HCC patients with and without portal hypertension were 29.1 kPa and 19.6 kPa, respectively (r = 0.26, p < 0.04). Liver stiffness was used to implement the Barcelona Clinic Liver Cancer algorithm in decisions about treatment. The authors concluded that the evaluation of liver fibrosis by transient elastography may be useful in the follow-up of patients with cirrhosis and a direct correlation with portal hypertension may aid in the evaluation of surgical risk in patients with HCC and in the choice of alternative therapies.

In a multi-center study, Barbero-Villares et al (2012) evaluated the presence of significant liver fibrosis by transient
elastography (FibroScan) in inflammatory bowel disease (IBD) patients treated with methotrexate. Cross-sectional study including IBD patients treated with methotrexate from different hospitals. Clinical and analytical data, duration of treatment, and cumulative dose of methotrexate were obtained. Liver stiffness was assessed by FibroScan. The cut-off value for significant liver fibrosis (according to METAVIR) was F greater than or equal to 2: 7.1 kPa. In the study, 46 patients were included, 30 women (65 %), with a mean age of 43 +/- 10 years; 31 patients had Crohn's disease (67.4 %), 13 ulcerative colitis (28.3 %), and 2 indeterminate colitis (4.3 %). The mean cumulative dose of methotrexate was 1,242 +/- 1,349 mg, with a mean treatment duration of 21 +/- 24 months. The mean value of liver stiffness was 4.7 +/- 6.9 kPa. There were 35 patients (76.1 %) with F01, 8 patients (17.4 %) with F = 2, and 3 patients with F greater than or equal to 3 (6.5 %). There were no differences in liver stiffness depending on sex, age, type of IBD, or cumulative dose of methotrexate. The authors concluded that (i) development of advanced liver fibrosis in IBD patients treated with methotrexate is exceptional, (ii) there were no differences in liver stiffness depending on the type of IBD or the cumulative dose of methotrexate, and (iii) FibroScan may be potentially useful for evaluation and follow-up of liver fibrosis in methotrexate-treated patients.

Lee and colleagues (2013) evaluated and compared the ability of serum HA and human cartilage glycoprotein-39 (YKL-40) values, as well as TE findings, to predict advanced hepatic fibrosis in a cohort from a single pediatric center. Subjects who underwent liver biopsy analysis within 12 months before enrollment were eligible for this prospective study. Hyaluronic acid and YKL-40 measurements were obtained within 1 month of TE. A METAVIR score of F3 or F4 was considered to indicate advanced fibrosis. A total of 128 patients (51 % males) aged 1.4 months to 27.6 years (22 % aged less than 2 years) were enrolled. Thirty-one subjects had data on HA and
YKL-40; and 97 subjects had data on both blood tests and TE. For the prediction of advanced fibrosis, the AUC values were 0.83 for TE, 0.72 for HA, and 0.52 for YKL-40. The AUC of 0.83 for TE was statistically significantly greater than the AUCs for HA (p = 0.03) and YKL-40 (p < 0.0001). Optimal cut-off points for predicting F3-F4 fibrosis were 8.6 kPa for TE (p < 0.0001), 43 ng/ml for HA (p < 0.0001), and 26.2 ng/ml for YKL-40 (p = 0.85). The combination of TE and HA was not better than TE alone for predicting advanced fibrosis (p = 0.15). The authors concluded that in this study, which evaluated TE, HA, and YKL-40 to predict liver fibrosis in children in the United States, YKL-40 had no predictive value and TE was superior to HA, but the addition of HA did not improve the performance of TE. They stated that these findings suggested that TE and HA may be useful non-invasive tools for assessing liver fibrosis in children.

An assessment of Fibroscan by the Institute for Clinical Effectiveness and Health Policy (IECS) (Pichon Riviere, et al., 2012) found: "There is evidence of good methodological quality from systematic reviews and meta-analysis of observational studies on diagnostic accuracy of transient elastography compared with the gold standard: biopsy. FibroScan seems to be a potential non-invasive diagnostic method used as an alternative to liver biopsy to diagnose and stage the degree of fibrosis. It might be useful in patients with contraindications for percutaneous biopsy and to follow-up patients with fibrosis who are under treatment. However, it has several disadvantages that may limit its reproducibility such as processes which increase or decrease liver consistency (steatosis), obesity, ascites or reduced intercostal spaces, and its low accuracy to identify mild to moderate stages of fibrosis. At present, the biopsy is still the diagnostic method of choice for the diagnosis of liver fibrosis.”

An assessment of transient elastography by Health Quality Ontario (Brener, 2015) concluded: “There was evidence to support the diagnostic accuracy of transient elastography
compared to liver biopsy for assessing liver fibrosis in the
disease areas of interest. There was evidence that the
diagnostic accuracy of FibroTest and acoustic force radiation
impulse were not significantly different from transient
elastography for assessing liver fibrosis in the disease areas of
interest. There was evidence to support the diagnostic
accuracy of controlled attenuation parameter compared to liver
biopsy for assessing steatosis in the disease areas of
interest. No evidence was found that assessed the clinical
utility of transient elastography (with or without controlled
attenuation parameter) versus biopsy, as measured by a
change in clinical diagnosis, treatment, or patient outcomes.
Beneficial impact could be presumed, given that the accuracy
of TE is comparable to that of a biopsy and would have an
impact as a noninvasive alternative to diagnose. The clinical
utility of CAP is less certain given that treatment for this
condition generally consists of providing advice about healthy
behaviours."

Guidelines on the management of hepatitis C from the
American Association for the Study of Liver Disease (2014)
state that "[n]on-invasive methods frequently used to estimate
liver disease severity include a liver-directed physical exam
(normal in most patients), routine blood tests (eg, serum
alanine transaminase, albumin, bilirubin, international
normalized ratio levels, and complete cell blood counts with
platelets), serum fibrosis marker panels, liver imaging (eg,
ultrasound, computed tomography scan), and liver
elastography.......Liver elastography can provide instant
information regarding liver stiffness at the point-of-care but can
only reliably distinguish cirrhosis from non-cirrhosis."

Transient Elastography for Detection of Esophageal
Varices in Individuals with Cirrhosis

Li and colleagues (2016) TE has been used for the prediction
of large esophageal varices in cirrhotic patients. However, the
conclusions have not been always consistent throughout the
different studies. These researchers performed a meta-analysis to evaluate the diagnostic accuracy of TE for the prediction of large esophageal varices. They performed a systematic literature search in PubMed, Embase, Web of Science, and CENTRAL in The Cochrane Library without time restriction. The strategy used was "(FibroScan or transient elastography or stiffness) and esophageal varices". Accuracy measures such as pooled sensitivity (SEN), specificity (SPE), among others, were calculated using Meta-DiSc statistical software. A total of 20 studies (2,994 patients) were included in this meta-analysis. The values of pooled SEN, SPE, positive and negative likelihood ratios (LRs) and DOR were as follows: 0.81 (95 % CI: 0.79 to 0.84), 0.71 (95 % CI: 0.69 to 0.73), 2.63 (95 % CI: 2.15 to 3.23), 0.27 (95 % CI: 0.22 to 0.34) and 10.30 (95 % CI: 7.33 to 14.47). The AUROC was 0.83. The Spearman correlation coefficient was 0.246 with a p-value of 0.296, indicating the absence of any significant threshold effects. In the subgroup analysis, the heterogeneity could be partially explained by the geographical origin of the study or etiology; or it could be partially explained blindly, through the appropriate interval and cut-off value of the LS. The authors concluded that TE could be used as a non-invasive screening tool for the prediction of large esophageal varices. However, since LS cut-off values varied throughout the different studies and significant heterogeneity also existed among them, there is a need for more reasonable approaches or flow diagram in order to improve the operability of this technology.

Pu and co-workers (2017) examined the diagnostic accuracy of FibroScan (FS) in detecting esophageal varices (EV) in cirrhotic patients. Through a systemic literature search of multiple databases, these investigators reviewed 15 studies using endoscopy as a reference standard, with the data necessary to calculate pooled SEN and SPE, positive and negative LRs, DOR and AUROC. The quality of the studies was rated by the Quality Assessment of Diagnostic Accuracy studies-2 tool. Clinical utility of FS for EV was evaluated by a
Fagan plot. Heterogeneity was explored using meta-regression and subgroup analysis. All statistical analyses were conducted via Stata12.0, MetaDisc1.4 and RevMan5. In 15 studies (n = 2,697), FS detected the presence of EV with the summary sensitivities of 84 % (95 % CI: 81.0 % to 86.0 %), specificities of 62 % (95 % CI: 58.0 % to 66.0 %), a positive LR of 2.3 (95 % CI: 1.81 to 2.94), a negative LR of 0.26 (95 % CI: 0.19 to 0.35), a DOR of 9.33 (95 % CI: 5.84 to 14.92) and an AUROC of 0.8262. FS diagnosed the presence of large EV with the pooled SEN of 0.78 (95 % CI: 75.0 % to 81.0 %), SPE of 0.76 (95 % CI: 73.0 % to 78.0 %), a positive and negative LR of 3.03 (95 % CI: 2.38 to 3.86) and 0.30 (95 % CI: 0.23 to 0.39), respectively, a summary diagnostic OR of 10.69 (95 % CI: 6.81 to 16.78), and an AUROC of 0.8321. A meta-regression and subgroup analysis indicated different etiology could serve as a potential source of heterogeneity in the diagnosis of the presence of EV group. A Deek’s funnel plot suggested a low probability for publication bias. The authors concluded that using FS to measure liver stiffness could not provide high accuracy for the size of EV due to the various cut-off and different etiologies. They stated that these limitations precluded widespread use in clinical practice at this time; therefore, the results should be interpreted cautiously given its SEN and SPE.

Transient Elastography for Diagnosis of Glycogenic Hepatopathy

Khoury and colleagues (2018) stated that glycogenic hepatopathy (GH) is a disorder associated with uncontrolled diabetes mellitus, most commonly type 1 (T1DM), expressed as right upper quadrant abdominal pain, hepatomegaly and increased liver enzymes. The diagnosis may be difficult, because laboratory and imaging tests are not pathognomonic. Although GH may be suggested based on clinical presentation and imaging studies, the gold standard for diagnosis is a liver biopsy, showing a significant accumulation of glycogen within the hepatocytes. Glycogenic hepatopathy may be diagnosed
also after elevated liver enzymes in routine blood tests; GH usually regresses after tight glycemic control. Progression to end-stage liver disease (ESLD) has never been reported. This review aimed to increase the awareness to this disease, to suggest a pathway for investigation that may reduce the use of unnecessary tests, especially invasive ones. These researchers carried out a PubMed database search (up to July 1, 2017) with the words "glycogenic hepatopathy", "hepatic glycogenosis", "liver glycogenosis" and "diabetes mellitus-associated glycogen storage hepatopathy". Articles in which diabetes mellitus-associated liver glycogen accumulation was described were included in this review. A total of 47 articles were found, describing 126 patients with GH. Hepatocellular disturbance was more profound than cholestatic disturbance. No synthetic failure was reported. The authors concluded that GH may be diagnosed conservatively, based on corroborating medical history, physical examination, laboratory tests, imaging studies and response to treatment, even without liver biopsy. In case of doubt about the diagnosis or lack of clinical response to treatment, a liver biopsy may be considered. These investigators stated that there is no role for non-invasive tests like FibroScan or FibroTest for the diagnosis of GH or for differentiation of this situation from NAFLD.

Sherigar and associates (2018) GH is a rare complication of the poorly controlled diabetes mellitus characterized by the transient liver dysfunction with elevated liver enzymes and associated hepatomegaly caused by the reversible accumulation of excess glycogen in the hepatocytes. It is predominantly observed in patients with longstanding T1DM and rarely reported in association with T2DM. Although it was first observed in the pediatric population, since then, it has been reported in adolescents and adults with or without ketoacidosis. The association of GH with hyperglycemia in diabetes has not been well-established. One of the essential elements in the pathophysiology of development of GH is the wide fluctuation in both glucose and insulin levels; GH and NAFLD are clinically indistinguishable, and the latter is more
prevalent in diabetic patients and can progress to advanced liver disease and cirrhosis. Gradient dual-echo MRI can distinguish GH from NAFLD; however, GH can reliably be diagnosed only by liver biopsy. Adequate glycemic control can result in complete remission of clinical, laboratory and histological abnormalities. There has been a recent report of varying degree of liver fibrosis identified in patients with GH. The authors concluded that further research is needed for an ideal non-invasive, rapid diagnostic test to avoid the extensive work-up and associated costs in evaluating suspected cases of GH. For now, a more aggressive pursuit of liver biopsy in the evaluation of elevated transaminases could identify additional cases of GH, allowing for continued elucidation of prevalence and natural history of this entity. Clinicians should also continue to pool patient data from case studies of patients with GH, to better understand the underlying risk factors and characteristics of this disease.

Transient Elastography for Diagnosis of Portal Hypertension

Kim and colleagues (2017) noted that TE has been proposed as a promising non-invasive alternative to hepatic venous pressure gradient (HVPG) for detecting portal hypertension (PH). However, previous studies have yielded conflicting results. These researchers gathered evidence on the clinical usefulness of TE versus HVPG for assessing PH. They conducted a systematic review by searching databases for relevant literature evaluating the clinical usefulness of non-invasive TE for assessing PH in patients with cirrhosis. A literature search in Ovid Medline, Embase and the Cochrane Library was performed for all studies published prior to December 30, 2015. A total of 8 studies (1,356 patients) met inclusion criteria. For the detection of PH (HVPG greater than or equal to 6 mmHg), the summary SEN and SPE were 0.88 (95 % CI: 0.86 to 0.90) and 0.74 (95 % CI: 0.67 to 0.81), respectively. Regarding clinically significant PH (HVPG greater than or equal to 10 mmHg), the summary SEN and
SPE were 0.85 (95 % CI: 0.63 to 0.97) and 0.71 (95 % CI: 0.50 to 0.93), respectively. The overall correlation estimate of TE and HVPG was large (0.75, 95 % CI: 0.65 to 0.82, p < 0.0001). The authors concluded that TE showed high accuracy and correlation for detecting the severity of PH. These investigators stated that TE showed promise as a reliable and non-invasive procedure for the evaluation of PH that should be integrated into clinical practice; however, further investigation is needed.

The authors stated that this study had several drawbacks. First, only 8 studies were used to evaluate the usefulness and performance of TE, thus limiting the robustness of the conclusions reached. Second, the characteristics of the included studies, including patient characteristics, cirrhosis etiologies and varying diagnostic thresholds, were not completely consistent. Third, these researchers included only studies written in English, thus language bias might have influenced the results.

In a retrospective study, Kumar and associates (2017) examined the diagnostic accuracy of TE for detecting clinically significant PH (CSPH) in patients with cirrhotic PH. This trial was conducted on consecutive patients with cirrhosis greater than 15 years of age who underwent HVPG and TE from July 2011 to May 2016. Correlation between HVPG and TE was analyzed using the Spearman's correlation test; ROC curves were prepared for determining the utility of TE in predicting various stages of PH. The best cut-off value of TE for the diagnosis of CSPH was obtained using the Youden index. The study included 326 patients (median age of 52 [range of 16 to 90] years; 81 % males). The most common etiology of cirrhosis was cryptogenic (45 %) followed by alcohol (34 %). The median HVPG was 16.0 (range of 1.5 to 30.5) mm Hg; 85 % of patients had CSPH. A significant positive correlation was noted between TE and HVPG (rho 0.361, p < 0.001). The AUROC curve for TE in predicting CSPH was 0.740 (95 % CI: 0.662 to 0.818) (p < 0.01). A cut-off value of TE of 21.6 kPa
best predicted CSPH with a PPV of 93%. The authors concluded that TE has a fair positive correlation with HVPG; thus, TE can be used as a non-invasive modality to evaluate the degree of PH. A cut-off TE value of 21.6 kPa identifies CSPH with a PPV of 93%. These investigators stated that as a non-invasive procedure, TE is a promising tool to translate into routine clinical practice for detecting CSPH. Moreover, they stated that further large prospective studies are needed to prospectively validate the findings of this study and also to examine if TE can be used in monitoring the hemodynamic response and the effect of drugs reducing portal pressure.

The authors stated that his study had 2 main drawbacks. First, it was a retrospective study, so the study may suffer from selection bias. These researchers included only those patients who underwent HVPG and TE during the study period; hence, the patients may not represent the entire population of patients with cirrhosis, as most included patients have moderate-to-severe PH. A prospective study design, which includes all consecutive patients of cirrhosis, regardless of degree of portal hypertension, would have been a better study design and more representative of the cirrhotic population of the community. Second, the lack of follow-up; follow-up data on complications of PH would have further validated these findings of TE cut-off for CSPH.

Transient Elastography for Prognosis of Chronic Hepatitis C

Erman and colleagues (2018) stated that CHC is a leading cause of hepatic fibrosis and cirrhosis. The level of fibrosis is traditionally established by histology, and prognosis is estimated using fibrosis progression rates (FPRs; annual probability of progressing across histological stages). However, newer non-invasive alternatives are quickly replacing biopsy. One alternative, TE, quantifies fibrosis by LSM. Given these developments, these researchers estimated prognosis in treatment-naïve CHC patients using
Noninvasive Tests for Hepatic Fibrosis

TE-based liver stiffness progression rates (LSPR) as an alternative to FPRs and compared consistency between LSPRs and FPRs. A systematic literature search was performed using multiple databases (January 1990 to February 2016); LSPRs were calculated using either a direct method (given the difference in serial LSMs and time elapsed) or an indirect method given a single LSM and the estimated duration of infection and pooled using random-effects meta-analyses. For validation purposes, FPRs were also estimated. Heterogeneity was explored by random-effects meta-regression. A total of 27 studies reporting on 39 groups of patients (n = 5,874) were identified with 35 groups allowing for indirect and 8 for direct estimation of LSPR. The majority (approximately 58%) of patients were HIV/HCV-co-infected. The estimated time-to-cirrhosis based on TE versus biopsy was 39 and 38 years, respectively. In univariate meta-regressions, male sex and HIV were positively and age at assessment, negatively associated with LSPRs. The authors concluded that non-invasive prognosis of HCV is consistent with FPRs in predicting time-to-cirrhosis, but more longitudinal studies of liver stiffness are needed to obtain refined estimates.

Transient Elastography for Diagnosis of Acute Cellular Rejection Following Liver Transplantation

Nacif and colleagues (2018) noted that TE is a non-invasive technique that measures liver stiffness. When an inflammatory process is present, this is shown by elevated levels of stiffness. Acute cellular rejection (ACR) is a consequence of an inflammatory response directed at endothelial and bile epithelial cells, and it is diagnosed through liver biopsy. In a systematic review, these investigators examined the viability of TE in ACR following liver transplantation. The Cochrane Library, Embase, and Medline PubMed databases were searched and updated to November 2016. The MESH terms used were "liver transplantation," "graft rejection," "elasticity imaging techniques" (PubMed), and "elastography" (Cochrane...
and Embase). A total of 70 studies were retrieved and selected using the PICO (patient, intervention, comparison or control, outcome) criteria; 3 prospective studies were selected to meta-analysis and evaluation. A total of 33 patients with ACR were assessed with TE. One study showed a cut-off point of greater than 7.9 kPa to define graft damage and less than 5.3 kPa to exclude graft damage (ROC 0.93; p < 0.001). Another study showed elevated levels of liver stiffness in ACR patients. However, in this study, no cut-off point for ACR was suggested. The final prospective study included 27 patients with ACR at liver biopsy. Cut-off points were defined as TE greater than 8.5 kPa, moderate-to-severe ACR, with a specificity of 100 % and ROC of 0.924. The measurement of TE of less than 4.2 kPa excluded the possibility of any ACR (p = 0.02). The authors concluded that TE may be an important tool for the severity of ACR in patients following liver transplantation; moreover, these researchers stated that further studies are needed to better define the cut-off points and applicability of this approach.

Magnetic Resonance Elastography

Magnetic resonance elastography (MRE) uses wave propagation and tissue deformation analysis to assess changes to tissue viscoelasticity caused by disease.14 It purportedly is based on principles similar to ultrasound transient elastography and acoustic radiation force impulse (ARFI); however, MRE supposedly assesses wave propagation and tissue displacement in three dimensions rather than one dimension.14 This form of imaging involves placing a probe against the individual’s back which emits low frequency vibrations that pass through the liver and can reportedly be measured by the MRI spin echo sequence.

Venkatesh et al (2013) stated that many pathological processes cause marked changes in the mechanical properties of tissue. MR elastography (MRE) is a non-invasive MRI based technique for quantitatively assessing the
mechanical properties of tissues in-vivo. Magnetic resonance elastography is performed by using a vibration source to generate low frequency mechanical waves in tissue, imaging the propagating waves using a phase contrast MRI technique, and then processing the wave information to generate quantitative images showing mechanical properties such as tissue stiffness. Since its first description in 1995, published studies have explored many potential clinical applications including brain, thyroid, lung, heart, breast, and skeletal muscle imaging. However, the best-documented application to emerge has been the use of MRE to assess liver disease. Multiple studies have demonstrated that there is a strong correlation between MRE-measured hepatic stiffness and the stage of fibrosis at histology. The emerging literature indicated that MRE can serve as a safer, less expensive, and potentially more accurate alternative to invasive liver biopsy, which is currently the gold standard for diagnosis and staging of liver fibrosis.

The British HIV Association’s guidelines on “The management of hepatitis viruses in adults infected with HIV 2013” (Wilkins et al, 2013) suggested hepatic transient elastography (TE) (FibroScan™ or ARFI) as the non-invasive investigation of choice (2B) but if unavailable, or when reliable TE readings are not obtained, a blood panel test (aspartate transaminase to platelet ratio index [APRI], FIB-4, enhanced liver fibrosis [ELF], Fibrometer™, Forns Index, FibroTest™) as an alternative (2C). It did not mention MR elastography as a management tool.

Tubb (2015) states that “Magnetic resonance elastography is an emerging MRI technology that provides sensitive and semi-quantitative assessment of tissue stiffness. The most promising clinical application for MR Elastography is the assessment of liver stiffness as a surrogate marker of liver disease and fibrosis.”
Furthermore, an UpToDate review on “Noninvasive assessment of hepatic fibrosis: Overview of serologic and radiographic tests” (Curry and Afdhal, 2015) states that “Radiologic methods for staging hepatic fibrosis are emerging as promising tools. The methods include ultrasound-based transient elastography, magnetic resonance elastography, acoustic radiation force impulse imaging, and cross-sectional imaging. Ultrasound-based transient elastography is the most studied radiologic method for staging hepatic fibrosis. When ultrasound-based transient elastography is used in a clinical setting, commonly used cutoffs for significant fibrosis and cirrhosis are >7 kPa and >11 to 14 kPa, respectively”.

Magnetic Resonance Elastography for Prediction of Ascites in Persons with Chronic Liver Disease

Abe and colleagues (2018) evaluated the utility of MRE as a non-invasive method for predicting ascites in patients with CLD. A total of 208 CLD patients underwent MRE to measure LS at the authors’ institution from March 2013 to June 2015 were included in this trial. These investigators evaluated the diagnostic performance of MRE for predicting the presence of ascites using ROC curve analysis and compared the performance with that of serum fibrosis markers. Multi-variate logistic regression analysis was performed to identify factors associated with the presence of ascites. The cumulative incidence of ascites was examined in patients without ascites at baseline. The pathological stage of liver fibrosis was evaluated in 81 CLD patients using histopathologic diagnosis. Of the 208 patients, 41 had ascites. The optimal cut-off LS value for the presence of ascites was 6.0 kPa (AU ROC curve = 0.87). The AUROC curve for the presence of ascites was significantly higher for MRE than that for fibrosis markers. Multi-variate analysis revealed that LS greater than 6.0 kPa was an independent risk factor for the presence of ascites. The cumulative incidence of ascites was significantly higher among those with LS values of greater than 6.0 kPa. There was significantly greater diagnostic accuracy for liver fibrosis
stage greater than or equal to 4 with MRE than that with fibrosis markers. The authors concluded that compared with serum fibrosis markers, MRE has higher diagnostic performance in predicting the presence of ascites. They stated that MRE-based LS has the potential to predict the presence of ascites in CLD patients.

Magnetic Resonance Elastography for Non-Alcoholic Steatohepatitis (NASH)

Park and associates (2017) stated that MRI techniques and US-based TE can be used in non-invasive diagnosis of fibrosis and steatosis in patients with NAFLD. In a prospective study, these researchers compared the performance of MRE versus TE for diagnosis of fibrosis, and MRI-based proton density fat fraction (MRI-PDFF) analysis versus TE-based controlled attenuation parameter (CAP) for diagnosis of steatosis in patients undergoing biopsy to assess NAFLD. They performed a cross-sectional study of 104 consecutive adults (56.7 % female) who underwent MRE, TE, and liver biopsy analysis (using the histologic scoring system for NAFLD from the Nonalcoholic Steatohepatitis Clinical Research Network Scoring System) from October 2011 through May 2016 at a tertiary medical center. All patients received a standard clinical evaluation, including collection of history, anthropometric examination, and biochemical tests. The primary outcomes were fibrosis and steatosis; secondary outcomes included dichotomized stages of fibrosis and NASH versus no NASH. Receiver operating characteristic curve analyses were used to compare performances of MRE versus TE in diagnosis of fibrosis (stages 1 to 4 versus 0) and MRI-PDFF versus CAP for diagnosis of steatosis (grades 1 to 3 versus 0) with respect to findings from biopsy analysis. MRE detected any fibrosis (stage 1 or more) with an area under the receiver operating characteristic curve (AUROC) of 0.82 (95 % CI: 0.74 to 0.91), which was significantly higher than that of TE (AUROC, 0.67; 95 % CI: 0.56 to 0.78). MRI-PDFF detected any steatosis with an AUROC of 0.99 (95 % CI: 0.98 to 1.00),
which was significantly higher than that of CAP (AUROC, 0.85; 95% CI: 0.75 to 0.96). MRE detected fibrosis of stages 2, 3, or 4 with AUROC values of 0.89 (95% CI: 0.83 to 0.96), 0.87 (95% CI: 0.78 to 0.96), and 0.87 (95% CI: 0.71 to 1.00); TE detected fibrosis of stages 2, 3, or 4 with AUROC values of 0.86 (95% CI: 0.77 to 0.95), 0.80 (95% CI: 0.67 to 0.93), and 0.69 (95% CI: 0.45 to 0.94). MRI-PDFF identified steatosis of grades 2 or 3 with AUROC values of 0.90 (95% CI: 0.82 to 0.97) and 0.92 (95% CI: 0.84 to 0.99); CAP identified steatosis of grades 2 or 3 with AUROC values of 0.70 (95% CI: 0.58 to 0.82) and 0.73 (95% CI: 0.58 to 0.89). The authors concluded that using prospective, head-to-head comparisons, they showed that MRI-based MRE and MRI-PDFF were significantly more accurate than ultrasound-based TE and CAP, respectively, for diagnosing fibrosis and steatosis in an American cohort of patients with biopsy-proven NAFLD. MRI-based techniques may be preferable to TE for accurate non-invasive assessment of NAFLD. Moreover, these researchers stated that future studies are needed to evaluate the clinical utility of MRI and TE for diagnosing fibrosis and steatosis in a multi-center, longitudinal design, both in observational and intervention studies. The cost-effectiveness of utilizing MRE versus TE and/or biopsy must also be evaluated to develop optimal diagnostic strategies for diagnosing NAFLD-associated fibrosis and steatosis.

The authors stated that this study had several drawbacks. The cross-sectional design of the study did not allow the assessment of MRE and TE for monitoring longitudinal changes in fibrosis. Since this was a single-center study in a highly specialized setting, the generalizability of its findings in other clinical settings was unknown. The median time interval between TE and biopsy was 107 days. A recent meta-analysis of paired liver biopsy studies has shown that the rate of fibrosis progression was slow, with an average progression of one stage to take 14.3 years in patients with NAFL and 7.1 years in patients with NASH. Thus, the time interval observed in this study was reasonable as fibrosis stage was unlikely to
change within a year. Furthermore, the analyses showed that the biopsy to imaging time interval did not affect the diagnostic accuracy of MRI and TE. Nevertheless, rapid changes in steatosis were possible, and ideally biopsy and imaging should be performed contemporaneously within 1 week, if feasible.

MRI-based techniques, including MRE and MRI-PDFF, were often expensive, although at the authors’ center the cost of MRE was lower than that of biopsy without the associated morbidity. Although TE was more widely available in some parts of the world, MRI techniques are more widely deployed in the United States, therefore MRE could also be made available on commercially available MRI platforms throughout the United States. While TE may be more useful for widespread screening, MRE may play a role in clinical trial assessments that require higher accuracy and precision.

These investigators stated that further studies are needed to evaluate the cost-effectiveness of MRI over TE for diagnosing NAFLD-related fibrosis and steatosis in before implementing these competing non-invasive approaches in routine clinical practice.

Besutti and colleagues (2019) stated that non-invasive tests to diagnose NASH are urgently needed. In a systematic review, these investigators examined imaging accuracy in diagnosing NASH among NAFLD patients, using liver biopsy as reference. Eligible studies were systematic reviews and cross-sectional/cohort studies of NAFLD patients comparing imaging with histology, considering accuracy and/or associations.

Medline, Scopus, Embase and Cochrane Library databases were searched up to April 2018. Studies were screened on title/abstract, then assessed for eligibility on full-text. Data were extracted using a pre-designed form. Risk of bias was assessed using Quality Assessment of Diagnostic Accuracy Studies-2 tool. Of the 641 studies screened, 61 were included in scoping review, 30 of which (with accuracy results) in data synthesis. Imaging techniques included: elastography (ARFI, MRE, TE), computed tomography (CT), MRI, scintigraphy and US. Histological NASH definition was heterogeneous. In
28/30 studies, no pre-specified threshold was used (high risk of bias). AUROCs were up to 0.82 for TE, 0.90 for ARFI, 0.93 for MRE and 0.82 for US scores. MR techniques with higher accuracy were spectroscopy (AUROC = 1 for alanine), susceptibility-weighted imaging (AUROC = 0.91), multi-parametric MRI (AUROC = 0.80), optical analysis (AUROC = 0.83), gadoxetic acid-enhanced MRI (AUROC = 0.85) and super-paramagnetic iron oxide-enhanced MRI (AUROC = 0.87). Results derived mostly from single studies without independent prospective validation. The authors concluded that there is currently insufficient evidence to support the use of imaging to diagnose NASH. These researchers stated that more studies are needed on US and MR elastography as well as non-elastographic techniques, to-date the most promising methods.

AASLD guidelines describe the role of magnetic resonance elastography (MRE) in identifying different degrees of fibrosis in patients with NAFLD, performing better than transient elastography for recognizing intermediate stage of fibrosis, but showing a same predictive value for advanced fibrosis stages (Lioni, et al., 2018). Therefore AASLD guidelines conclude that MRE and transient elastography are both useful tools for identifying NAFLD patients with advanced liver fibrosis.

Acoustic Radiation Force Impulse (ARFI)

Acoustic radiation forced impulse (ARFI) (e.g., Virtual Touch Imaging – Acuson S2000-3000) relies on short-duration, high-intensity acoustic pulses to quantify the mechanical properties of tissues, without manual compression, by measuring shear wave velocity induced by acoustic radiation and propagated in the tissue. This technique purportedly provides single one-dimensional measures of tissue elasticity, although the area can be positioned on a two-dimensional B mode image. The measurements are expressed as m/s, which supposedly indicates the shear wave speed traveling perpendicular to the shear wave source.
An assessment of ARFI by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2016) found that studies were "favourable to the use of ARFI in hepatitis C", but "[n]o literature was identified regarding evidence-based guidelines and clinical effectiveness on ARFI compared with liver biopsy in patients with Hepatitis C". The review cited an economic analysis that found that ARFI was dominated by less costly and more effective options among chronic hepatitis C patients.

**Plasma Cytokeratin-18**

Castera and co-workers (2013) noted that a common clinical concern in patients with NAFLD is whether they have NASH or simple steatosis and, more importantly, what the stage of fibrosis is and whether the level of fibrosis has increased over time. Such concern is based on the fact that patients with NAFLD with advanced fibrosis are at greatest risk of developing complications of end-stage liver disease. Although it lacks sensitivity, ultrasonography is an accepted tool for steatosis screening. The controlled attenuation parameter (CAP) seems a promising screening technique, but requires further validation. Cytokeratin-18 (CK-18) has been extensively validated, but it is an imperfect serum marker of NASH. Ultrasonography-based TE can exclude advanced fibrosis and cirrhosis, but its main limitation is its reduced applicability in patients with NAFLD, which is not completely solved by use of the XL probe. Of the non-invasive serum markers, the NAFLD fibrosis score is the most validated and has appropriate accuracy in distinguishing patients with and without advanced fibrosis. The authors concluded that although non-invasive methods require further validation, they could be useful for selecting those patients with NAFLD who require a liver biopsy.

Cusi and associates (2014) stated that liver biopsy is the only reliable way of diagnosing and staging NASH but its invasive nature limits its use. Plasma caspase-generated CK-18 fragments have been proposed as a non-invasive alternative.
These researchers studied its clinical value in a large multi-ethnic NAFLD population and examined its relationship to clinical/metabolic/histological parameters. A total of 424 middle-aged subjects were included in this study – these investigators measured adipose tissue, liver and muscle insulin resistance (IR), liver fat by magnetic resonance spectroscopy (MRS; n = 275) and histology (n = 318). Median CK-18 were elevated in patients with versus without NAFLD by MRS (209 [IQR: 137 to 329] versus 122 [IQR: 98 to 155]U/L) or with versus without NASH (232 [IQR: 151 to 387] versus 170 [IQR: 135 to 234]U/L, both p < 0.001). Plasma CK-18 raised significantly with any increase in steatosis, inflammation and fibrosis, but there was a significant overlap across disease severity. The CK-18 AUROC to predict NAFLD, NASH or fibrosis were 0.77 (95 % CI: 0.71 to 0.84), 0.65 (95 % CI: 0.59 to 0.71) and 0.68 (95 % CI: 0.61 to 0.75), respectively. The overall sensitivity/specificity for NAFLD, NASH and fibrosis were 63 % (57 to 70 %)/83 % (69 to 92 %), 58 % (51 to 65 %)/68 % (59 to 76 %) and 54 % (44 to 63 %)/85 % (75 to 92 %), respectively. CK-18 correlated most strongly with ALT (r = 0.57, p < 0.0001) and adipose tissue IR (insulin-suppression of FFA: r = -0.43; p < 0.001), less with steatosis, lobular inflammation and fibrosis (r = 0.28 to 0.34, all p < 0.001), but not with ballooning, BMI, metabolic syndrome or type 2 diabetes mellitus. The authors concluded that plasma CK-18 has a high specificity for NAFLD and fibrosis, but its limited sensitivity makes it inadequate as a screening test for staging NASH. Whether combined as a diagnostic panel with other biomarkers or clinical/laboratory tests may prove useful requires further study.

Kwok and colleagues (2014) reviewed current literature on the use of non-invasive tests to assess the severity of NAFLD. These researchers performed a systematic literature searching identified studies evaluating non-invasive tests of NASH and fibrosis using liver biopsy as the reference standard. Meta-analysis was performed for areas with adequate number of publications. Serum tests and physical measurements like TE
have high NPV in excluding advanced fibrosis in NAFLD patients. The NAFLD fibrosis score comprises of 6 routine clinical parameters and has been endorsed by current American guidelines as a screening test to exclude low-risk individuals. The pooled sensitivities and specificities for TE to diagnose F ≥ 2, F ≥ 3 and F4 disease were 79 % and 75 %, 85 % and 85 %, and 92 % and 92 %, respectively. Liver stiffness measurement often fails in obese patients, but the success rate can be improved with the use of the XL probe. A number of biomarkers have been developed for the diagnosis of NASH, but few were independently validated. Serum/plasma CK-18 fragments have been most extensively evaluated and have a pooled sensitivity of 66 % and specificity of 82 % in diagnosing NASH. The authors concluded that current non-invasive tests are accurate in excluding advanced fibrosis in NAFLD patients, and may be used for initial assessment. Moreover, they stated that further development and evaluation of NASH biomarkers are needed.

Furthermore, an UpToDate review on “Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults” (Sheth and Chopra, 2015) does not mention plasma cytokeratin-18 as a diagnostic tool.

**Hepatic Artery Resistive Index for Evaluation of Fibrosis Progression in Individuals with NAFLD**

Tana and colleagues (2018) stated that US can reveal the presence of steatosis in NAFLD, but its diagnostic accuracy to reveal signs of fibrosis is low except in advanced stages of disease (e.g., cirrhosis). Current guidelines suggest the use of clinical algorithms, such as the NAFLD fibrosis score, and elastography to predict the progression of fibrosis, and the integration of elastography improves the detection accuracy of LS. However, there is a lack of evidence about the correlation between clinical algorithms and conventional US, and elastography is limited by the relative low diffusion, necessity of training, and loss of diagnostic accuracy in patients with
high BMI, waist circumference, or increased thickness of parietal walls, with consequent significant rates of failure of measurement of LS. Recently, the measurement of hepatic artery resistive index (HARI) has demonstrated a significant positive correlation with fibrosis degree, as measured with NAFLD fibrosis score, suggesting that the fibrous tissue accumulation may result in increased arterial rigidity and, thus, in a rise of resistance to flow, and that the different tissue composition of the liver (adipose versus fibrous) can influence HARI differently. These investigators stated that these issues should be further examined because some aspects are still unknown. The limited data currently justify the need of larger, prospective studies aimed at examining if HARI correlates with elastography results. In view of their effect on weight loss, serum lipid concentration, and hepatic arterial flow hemodynamics, it could be interesting to evaluate if lifestyle and diet changes can influence significantly HARI values in NAFLD patients.

Serum Angiotensin Converting Enzyme for Liver Fibrosis

Akar and colleagues (2018) examined if any possible relationship between serum angiotensin-converting enzyme (ACE) levels and the stages of liver fibrosis in patients with CHC. A total 100 CHC and 100 healthy subjects were enrolled in this study. The relationship between serum ACE level and the stages liver fibrosis was investigated using 3 different formats: group G-I, classic Ishak's Score from F1 to F6; group G-II, mild [F1-2], moderate [F3-4] and severe [F5-6]; and group G-III, mild [less than or equal to F2] and advanced [F greater than 2]. The clinical usability of serum ACE level for both groups was also investigated. Median serum ACE levels were higher in the healthy group than in CHC (42.5 [7 to 119] versus 36 [7 to 91] U/I, p = 0.002). There was no statistical difference among the 3 different fibrosis groups (G-I, G-II, G-III, p = 0.797, p = 0.986, and p = 0.874) and no correlation between serum ACE level and the stages of liver fibrosis (r = 0.026, p = 0.923). The usability of serum ACE for evaluated
patients with CHC and healthy subjects were calculated as 47 % and 64 %, respectively. The authors concluded that the findings of this study indicated that there was no relationship or correlation between serum ACE levels and stages of liver fibrosis in patients with CHC.

Serum miR-29a and miR-122 for Diagnosis of Non-Alcoholic Fatty Liver Disease

Jampoka and colleagues (2018) stated that NAFLD is an over accumulation of triglyceride in the liver without alcohol consumption, which its major cause is from insulin resistance. Patients with NAFLD can develop liver fibrosis, cirrhosis and HCC. MicroRNAs (miRNAs) are non-coding RNAs that regulate post-transcriptional gene silencing. Previous research reported that miR-29 family (a, b and c) and miR-122 have an important role in regulating insulin resistance related to NAFLD. These investigators examined if miR-29 and miR-122 can be possible biomarkers for non-invasive diagnosis of NAFLD. Serum samples were collected from 58 NAFLD patients and 34 healthy controls; miRNAs were extracted from serum by using miRNA purification kit followed by polyuridylation, reverse transcription and quantitative real-time PCR. Furthermore, these researchers analyzed the correlation between miR-29 and miR-122 and level of liver inflammation in NAFLD patients. They found that serum miR-29a levels in NAFLD patients were significantly lower (p = 0.006) than the control group, while miR-29c levels were unchanged, and miR-29b levels were undetectable. However, these researchers found that serum miR-122 levels in NAFLD patients were significantly higher (p < 0.001) than those found in the control group. For miR-29a, the area under curve (AUC) was 0.679 (p = 0.0065) with 60.87 % sensitivity and 82.35 % specificity. For miR-122, the AUC was 0.831 (p < 0.0001) with 75.00 % sensitivity and 82.35 % specificity. Interestingly, the level of serum miR-122 were significantly different between patients with not steatohepatitis (NAFLD Activity Score [NAS] of less than 4) and steatohepatitis (NAS of greater than or
equal to 4), indicating that the levels of miR-122 were related to the severity of NAFLD. The authors concluded that serum levels of miR-29a and miR-122 might be possible biomarkers for non-invasive diagnosis of NAFLD.

Serum miRNA-221 and miRNA-222 for Progression of Liver Fibrosis

Abdel-Al and colleagues (2018) attempted to find highly specific and sensitive miRNA biomarkers that can be used to detect different stages of liver fibrosis. The trial entailed 42 cases of CHC with early-stage fibrosis, 45 cases of CHC with late-stage fibrosis, and 40 healthy subjects with no CHC or fibrosis as controls. Expression patterns of 5 miRNAs (miR-16, miR-146a, miR-214-5p, miR-221, and miR-222) were analyzed in each group using TaqMan real-time PCR. Serum levels of miRNA-16, miRNA-146a, miRNA-221, and miRNA-222 were all significantly up-regulated in early and late stages of liver fibrosis; miRNA-222 had the highest sensitivity and specificity values in early and late fibrosis; miRNA-221 had the 2nd highest sensitivity and specificity with the late-stage fibrosis group. Furthermore, miRNA-221 showed significant positive correlations with both miRNA-16 and miRNA-146a in the early- and late-stage fibrosis groups, with the early stage having a stronger correlation. The authors concluded that these findings indicated that miRNA-16, miRNA-146a, miRNA-221, and miRNA-222 can be used to detect the presence of liver fibrosis. They stated that the high sensitivity and specificity of miRNA-222 and miRNA-221 in late-stage fibrosis indicated promising prognostic biomarkers for HCV-induced liver fibrosis.

Ultrasound Elastography for Screening Portal Hypertension-Related Complications in Children

In a systematic review and meta-analysis, Kim and colleagues (2019) examined the diagnostic performance of US elastography in evaluating portal hypertension in children and
compared the liver and spleen stiffness values between the portal hypertension and control groups. Studies in the Medline and Embase databases were selected that investigated the diagnostic performance of US elastography in children with portal hypertension up to December 21, 2017. Pooled sensitivity and specificity data were assessed by hierarchical logistic regression modeling. A total of 11 studies were included in the systematic review, and a meta-analysis could be conducted in 7 of these publications to evaluate the diagnostic performance of US elastography. The summary sensitivity and specificity of this method for liver stiffness were 90% (95% CI: 83% to 94%) and 79% (95% CI: 73% to 84%), respectively, and the AUROC was 0.92 (95% CI: 0.90 to 0.94). A subgroup analysis of 5 TE studies revealed similar diagnostic performance (sensitivity, 90%; specificity, 78%). In 10 of the 11 studies that examined liver stiffness and 2 of the 3 studies that also measured spleen stiffness, patients in the portal hypertension group had a significantly higher stiffness value than the control group (p < 0.05). The authors concluded that US elastography exhibited good performance in diagnosing portal hypertension and could identify significant differences in liver and spleen stiffness in children with this condition. These researchers stated that this method thus has considerable potential as a non-invasive tool for screening portal hypertension-related complications in children with chronic liver disease.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient elastography (e.g., FibroScan):</td>
<td></td>
</tr>
</tbody>
</table>

CPT codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76981</td>
<td>Ultrasound, elastography; parenchyma (eg, organ)</td>
</tr>
<tr>
<td>91200</td>
<td>Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>76982</td>
<td>Ultrasound, elastography</td>
</tr>
<tr>
<td>76983</td>
<td>Ultrasound, elastography</td>
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ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>E83.110</td>
<td>Hereditary hemochromatosis</td>
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ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>E74.00 - E74.09</td>
<td>Glycogen storage disease [glycogenic hepatopathy]</td>
</tr>
<tr>
<td>I85.00 - I85.01</td>
<td>Esophageal varices</td>
</tr>
<tr>
<td>K76.6</td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>T86.41</td>
<td>Liver transplant rejection</td>
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</table>

FibroTest-ActiTest and HCV-FibroSure:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0001M</td>
<td>Infectious disease, HCV, 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</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>81596</td>
<td>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</td>
</tr>
</tbody>
</table>

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>47000</td>
<td>Biopsy of liver, needle; percutaneous</td>
</tr>
<tr>
<td>47001</td>
<td>Biopsy of liver, needle; when done for indicated purpose at time of other major procedure (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>47100</td>
<td>Biopsy of liver, wedge</td>
</tr>
<tr>
<td>91200</td>
<td>Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report</td>
</tr>
</tbody>
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ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B18.0</td>
<td>Chronic viral hepatitis B</td>
</tr>
<tr>
<td>B18.1</td>
<td>Chronic viral hepatitis C</td>
</tr>
<tr>
<td>B18.2</td>
<td>Chronic viral hepatitis C</td>
</tr>
<tr>
<td>E83.110</td>
<td>Hereditary hemochromatosis</td>
</tr>
<tr>
<td>K70.0</td>
<td>Diseases of liver [chronic]</td>
</tr>
<tr>
<td>K77</td>
<td>Diseases of liver [chronic]</td>
</tr>
<tr>
<td>Z94.4</td>
<td>Liver transplant status</td>
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</tbody>
</table>

**Magnetic Resonance Elastography:**

CPT codes covered if selection criteria are met:

<table>
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<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76391</td>
<td>Magnetic resonance (eg, vibration) elastography</td>
</tr>
</tbody>
</table>

Enhanced Liver Fibrosis (ELF) test:
### CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0014M</td>
<td>Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PⅢⅠNⅠP], 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</td>
</tr>
</tbody>
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### ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>K70.0 - K77</td>
<td>Diseases of liver [chronic]</td>
</tr>
</tbody>
</table>

### Serum marker tests:

### CPT codes not covered for indications listed in the CPB:

**Hepatic artery resistive index, serum markers tests angiotensin converting enzyme, serum miR-29a and miR-122 and serum miRNA-221 and miRNA-222 - no specific code [not covered for liver Fibrosis]:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0166U</td>
<td>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</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>83520</td>
<td>Immunoassay, analyte, quantitative; not otherwise specified [If billed for FIBROspect or HCV-FIBROSUREFibroMAX, FibroTest-ActiTest, HepaScore]</td>
</tr>
<tr>
<td>83883</td>
<td>Nephelometry, each analyze not elsewhere specified [If billed for FIBROspect or HCV-FIBROSUREFibroMAX, HepaScore]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure [for the evaluation of non-alcoholic fatty liver disease and other liver disease]</td>
</tr>
</tbody>
</table>

Other CPT codes related to the CPB:

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<td>Biopsy of liver, needle; when done for indicated purpose at time of other major procedure (List separately in addition to code for primary procedure)</td>
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<tr>
<td>47100</td>
<td>Biopsy of liver, wedge</td>
</tr>
<tr>
<td>82977</td>
<td>Glutamyltransferase, gamma (GGT)</td>
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</tbody>
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ICD-10 codes covered if selection criteria are met:

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<th>Code Description</th>
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<tr>
<td>K77</td>
<td>Diseases of liver [chronic]</td>
</tr>
<tr>
<td>Z94.4</td>
<td>Liver transplant status</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

Acoustic Radiation Force Impulse

1. Canadian Agency for Drugs and Technologies in Health (CADTH). Acoustic Radiation Force Impulse Imaging for Diagnosis and Monitoring of Liver Fibrosis in Patients


Enhanced Liver Fibrosis (ELF) Test


Hepatic Artery Resistive Index


Magnetic Resonance Elastography


Serum Markers


15. Cusi K, Chang Z, Harrison S, et al. Limited value of plasma cytokeratin-18 as a biomarker for NASH and


57. Sheth SG, Chopra S. Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults. UpToDate Inc., Waltham, MA. Last reviewed June 2015.


Transient Elastography (FibroScan)


16. Darus PN. FibroScan. Technology Review. Putrajaya, Malaysia: Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia (MaHTAS); June 2008.


41. Pesce A, Scilletta R, Branca A, et al. Does transient elastography (FibroScan®) have a role in decision


49. Sheth SG, Chopra S. Epidemiology, clinical features, and diagnosis of nonalcoholic steatohepatitis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2012.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0690 Noninvasive Tests for Hepatic Fibrosis

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania

revised 06/08/2020