MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Noninvasive Techniques for the Evaluation and Monitoring of Patients with Chronic Liver Disease

Table of Contents

Policy Number: 921

BCBSA Reference Number: 2.04.41
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

A single FibroSURE multianalyte assay may be considered **MEDICALLY NECESSARY** for the evaluation of patients with chronic liver disease.

FibroSURE multianalyte assays are considered **INVESTIGATIONAL** for monitoring of patients with chronic liver disease.

Other multianalyte assays with algorithmic analyses are considered **INVESTIGATIONAL** for the evaluation or monitoring of patients with chronic liver disease.

Transient elastography (FibroScan) imaging may be considered **MEDICALLY NECESSARY** for the evaluation of patients with chronic liver disease.

Transient elastography (FibroScan) imaging is considered **INVESTIGATIONAL** for monitoring of patients with chronic liver disease.

The use of other noninvasive imaging, including but not limited to, acoustic radiation force impulse imaging (ARFI; eg, Acuson S2000), or real-time tissue elastography, is considered **INVESTIGATIONAL** for the evaluation or monitoring of patients with chronic liver disease.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue℠	Prior authorization is **not required**.
Medicare PPO Blue℠	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
0002M	Liver disease, 10 biochemical assays (ALT, A2-macroglobulin, apolipoprotein A1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis, and alcoholic steatohepatitis (ASH)
0003M	Liver disease, 10 biochemical assays (ALT, A2-macroglobulin, apolipoprotein A1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis, and nonalcoholic steatohepatitis (NASH)
81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
91200	Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report

According to the policy statement above, the following CPT codes are considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
76981	Ultrasound, elastography; parenchyma (eg, organ)

76982	Ultrasound, elastography; first target lesion
76983	Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure)

DESCRIPTION

Biopsy for Chronic Liver Disease

The diagnosis of non-neoplastic liver disease is often made from needle biopsy samples. In addition to establishing a disease etiology, liver biopsy can determine the degree of inflammation present and can stage the degree of fibrosis. The degree of inflammation and fibrosis may be assessed by different scoring schemes. Most of these scoring schemes grade inflammation from 0 (no or minimal inflammation) to 4 (severe) and fibrosis from 0 (no fibrosis) to 4 (cirrhosis). There are several limitations to liver biopsy, including its invasive nature, small tissue sample size, and subjective grading system. Regarding small tissue sample size, liver fibrosis can be patchy and thus missed on a biopsy sample, which includes only 0.002% of the liver tissue. A noninvasive alternative to liver biopsy would be particularly helpful, both to initially assess patients and then to monitoring response to therapy. The implications of using liver biopsy as a reference standard are discussed in the Rationale.

Hepatitis C Virus

Infection with HCV can lead to permanent liver damage. Prior to noninvasive testing, liver biopsy was typically recommended before the initiation of antiviral therapy. Repeat biopsies may be performed to monitor fibrosis progression. Liver biopsies are analyzed according to a histologic scoring system; the most commonly used one for HCV is the Metavir scoring system, which scores the presence and degree of inflammatory activity and fibrosis. The fibrosis is graded from F0 to F4, with a Metavir score of F0 signifying no fibrosis and F4 signifying cirrhosis (which is defined as the presence throughout the liver of fibrous septa that subdivide the liver parenchyma into nodules and represents the final and irreversible form of the disease). The stage of fibrosis is the most important single predictor of morbidity and mortality in patients with hepatitis C. Biopsies for HCV are also evaluated according to the degree of inflammation present, referred to as the grade or activity level. For example, the Metavir system includes scores for necroinflammatory activity ranging from A0 to A3 (A0 = no activity, A1 = minimal activity, A2 = moderate activity, A3 = severe activity).

Hepatitis B Virus

Most people who become infected with theHBV recover fully, but a small portion develops chronic HBV, which can lead to permanent liver damage. As with HCV, identification of liver fibrosis is needed to determine timing and management of treatment, and liver biopsy is the criterion standard for staging fibrosis. The grading of fibrosis in HBV also uses the Metavir system.

Alcoholic Liver Disease

ALD is the leading cause of liver disease in most Western countries. Histologic features of ALD usually include steatosis, alcoholic steatohepatitis, hepatocyte necrosis, Mallory bodies (tangled proteins seen in degenerating hepatocytes), a large polymorphonuclear inflammatory infiltrate, and, with continued alcohol abuse, fibrosis, and possibly cirrhosis. The grading of fibrosis is similar to the scoring system used in HCV. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

Nonalcoholic Fatty Liver Disease

NAFLD is defined as a condition that pathologically resembles ALD but occurs in patients who are not heavy users of alcohol. Moreover, NAFLD may be associated with a variety of conditions, including obesity, diabetes, and dyslipidemia. The characteristic feature of NAFLD is steatosis. At the benign end of the disease spectrum, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, nonalcoholic steatohepatitis (NASH), which shows overlapping histologic features with ALD, is an intermediate form of liver damage, and liver biopsy may show steatosis, Mallory bodies, focal inflammation, and degenerating hepatocytes. NASH can progress to fibrosis and cirrhosis. A variety of histologic scoring systems have been used to evaluate NAFLD. The NAFLD Activity Score system for NASH includes scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2). Cases with scores of 5 or greater are considered NASH, while cases with scores of 3 and 4 are considered

borderline (probable or possible) NASH. The grading of fibrosis is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.
Noninvasive Alternatives to Liver Biopsy

Multianalyte Assays
A variety of noninvasive laboratory tests are being evaluated as alternatives to liver biopsy. Biochemical tests can be broadly categorized into indirect and direct markers of liver fibrosis. Indirect markers include liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), the ALT/AST ratio (also referred to as the AAR), platelet count, and prothrombin index. There has been a growing understanding of the underlying pathophysiology of fibrosis, leading to a direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is the activation of the hepatic stellate cell. Normally, stellate cells are quiescent but are activated in the setting of liver injury, producing a variety of extracellular matrix (ECM) proteins. In normal livers, the rate of ECM production equals its degradation, but with fibrosis, production exceeds degradation. Metalloproteinases are involved in intracellular degradation of ECM, and a profibrogenic state exists when there is either a down-regulation of metalloproteinases or an increase in tissue inhibitors of metalloproteinases. Both metalloproteinases and tissue inhibitors of metalloproteinases can be measured in the serum, which directly reflects the fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or α_2-macroglobulin.

While many studies have been done on these individual markers, or on groups of markers in different populations of patients with liver disease, there has been interest in analyzing multiple markers using mathematical algorithms to generate a score that categorizes patients according to the biopsy score. It is proposed that these algorithms can be used as alternatives to liver biopsy in patients with liver disease. The following proprietary, algorithm-based tests are commercially available in the U. S.

FibroSURE

HCV FibroSURE
The HCV FibroSURE uses a combination of six serum biochemical indirect markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver that corresponds to the Metavir scoring system for stage (ie, fibrosis) and grade (ie, necroinflammatory activity). The measures are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The biochemical markers include the readily available measurements of α_2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase, ALT, and apolipoprotein AI. Developed in France, the test has been clinically available in Europe under the name FibroTest since 2003; it is exclusively offered by LabCorp in the U. S. as HCV FibroSURE.

ASH FibroSURE
ASH FibroSURE (ASH Test) uses a combination of ten serum biochemical markers of liver function together with age, sex, height, and weight in a proprietary algorithm; the test is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and ASH. The biochemical markers include α_2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, γ-glutamyl transpeptidase, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name AshTest™ (BioPredictive); the test is exclusively offered by LabCorp in the U. S. as ASH FibroSURE.

NASH FibroSURE
NASH FibroSURE (NASH Test) uses a proprietary algorithm of the same ten biochemical markers of liver function in combination with age, sex, height, and weight and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and NASH. The biochemical markers include α_2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, γ-glutamyl transpeptidase, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name NashTest™ (BioPredictive); the test is exclusively offered by LabCorp in the U. S. as NASH FibroSURE.

FIBROSpect II
FIBROSpect II uses a combination of three markers that directly measure fibrogenesis of the liver, analyzed with a patented algorithm. The markers include hyaluronic acid, tissue inhibitor of metalloproteinase 1, and α_2-macroglobulin. FIBROSpect II is offered exclusively by Prometheus Laboratories. The measures are combined using a logistic regression algorithm to generate a FIBROSpect II index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.

Noninvasive Imaging Technologies
Noninvasive imaging technologies to detect liver fibrosis or cirrhosis among patients with chronic liver disease are being evaluated as alternatives to liver biopsy. The noninvasive imaging technologies include transient elastography (eg, FibroScan), magnetic resonance elastography, acoustic radiation force impulse (ARFI) imaging (eg, Acuson S2000), and real-time tissue elastography (eg, HI VISION Preirus). Noninvasive imaging tests have been used in combination with multianalyte serum tests such as FibroTest or FibroSURE with FibroScan.

Transient Elastography
Transient elastography (FibroScan) uses a mechanical vibrator to produce mild amplitude and low-frequency (50 Hz) waves, inducing an elastic shear wave that propagates throughout the liver. Ultrasound tracks the wave, measuring its speed in kilopascals, which correlates with liver stiffness. Increases in liver fibrosis also increase liver stiffness and resistance of liver blood flow. Transient elastography does not perform as well in patients with ascites, higher body mass index, or narrow intercostal margins. Although FibroScan may be used to measure fibrosis (unlike liver biopsy), it does not provide information on necroinflammatory activity and steatosis, nor is it accurate during acute hepatitis or hepatitis exacerbations.

ARFI Imaging
ARFI imaging uses an ultrasound probe to produce an acoustic “push” pulse, which generates shear waves that propagate in tissue to assess liver stiffness. ARFI elastography evaluates the wave propagation speed (measured in meters per second) to assess liver stiffness. The faster the shear wave speed, the harder the object. ARFI technologies include Virtual Touch Quantification and Siemens Acuson S2000 system. ARFI elastography can be performed at the same time as a liver sonographic evaluation, even in patients with a significant amount of ascites.

Magnetic Resonance Elastography
Magnetic resonance elastography uses a driver to generate 60-Hz mechanical waves on the patient’s chest wall. The magnetic resonance equipment creates elastograms by processing the acquired images of propagating shear waves in the liver using an inversion algorithm. These elastograms represent the shear stiffness as a pixel value in kilopascals. Magnetic resonance elastography has several advantages over ultrasound elastography, including: (1) the ability to analyze larger liver volumes; (2) the ability to analyze liver volumes of obese patients or patients with ascites; and (3) the ability to precisely analyze viscoelasticity using a 3-dimensional displacement vector.

Real-Time Tissue Elastography
Real-time tissue elastography is a type of strain elastography that uses a combined autocorrelation method to measure tissue strain caused by manual compression or a person’s heartbeat. The relative tissue strain is displayed on conventional color B mode ultrasound images in real-time. Hitachi manufactures real-time tissue elastography devices, including the HI VISION Preirus. The challenge is to identify a region of interest while avoiding areas likely to introduce artifacts, such as large blood vessels, the area near the ribs, and the surface of the liver. Areas of low strain increase as fibrosis progresses and strain distribution becomes more complex. Various subjective and quantitative methods have been developed to evaluate the results. Real-time tissue elastography can be performed in patients with ascites or inflammation. This technology does not perform as well in severely obese individuals.

Summary

Noninvasive techniques to monitor liver fibrosis are being investigated as alternatives to liver biopsy in patients with chronic liver disease. There are two options for noninvasive monitoring: (1) multianalyte serum assays with algorithmic analysis of either direct or indirect biomarkers; and (2) specialized radiologic methods, including magnetic resonance elastography, transient elastography, acoustic radiation force impulse imaging, and real-time transient elastography.

Multianalyte Serum Assays

For individuals who have chronic liver disease who receive FibroSURE serum panels, the evidence includes systematic reviews of more than 30 observational studies (>5000 patients). The relevant outcomes are test validity, morbid events, and treatment-related morbidity. FibroSURE has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are established cutoffs, although they were not consistently used in validation studies. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, FibroSURE results provide data sufficiently useful to determine therapy. Specifically, FibroSURE has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in several randomized controlled trials that showed the efficacy of hepatitis C virus treatments, which in turn demonstrated the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic liver disease who receive multianalyte serum assays for liver function assessment other than FibroSURE, the evidence includes systematic reviews of observational studies. The relevant outcomes are test validity, morbid events, and treatment-related morbidity. Studies have frequently included varying cutoffs, some of which were standardized, and others not validated. Cut-off thresholds have often been modified over time, may be specific to certain patient populations, and in some cases, guideline recommendations differ from cut-offs designated by manufacturers and those utilized in studies.Other multianalyte serum tests (eg, aminotransferase to platelet ratio index, fibrosis-4) lack data on clinical validity and utility. There does not appear to be evidence of incremental benefit over clinical assessment using the individual laboratory assay components. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other multianalyte serum assays improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Noninvasive Imaging

For individuals who have chronic liver disease who receive transient elastography, the evidence includes many systematic reviews of more than 50 observational studies (>10000 patients). The relevant outcomes are test validity, morbid events, and treatment-related morbidity. Transient elastography (FibroScan) has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are varying cutoffs for positivity. Failures of the test are not uncommon, particularly for those with high body mass index, but these failures often went undetected in analyses of the validation studies. Given these limitations and the imperfect reference standard, it can be difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, the FibroScan results provide data sufficiently useful to determine therapy. In fact, FibroScan has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in the participants of several randomized controlled trials. These trials showed the efficacy of hepatitis C virus treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic liver disease who receive noninvasive radiologic methods other than transient elastography for liver fibrosis measurement, the evidence includes systematic reviews of observational studies. The relevant outcomes are test validity, morbid events, and treatment-related morbidity. Other radiologic methods (eg, magnetic resonance elastography, real-time transient elastography, acoustic radiation force impulse imaging) may have similar performance for detecting

significant fibrosis or cirrhosis. Studies have frequently included varying cutoffs not prespecified or validated. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other noninvasive radiologic methods improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

Date	Action
6/2020	Clarified coding information.
1/2020	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged. Clarified coding information.
12/2019	Code 76391 Magnetic resonance (eg, vibration) elastography removed. Effective 12/9/2019.
1/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged. Clarified coding information.
1/2018	New references added from BCBSA National medical policy.
10/2017	Clarified coding information.
5/2017	BCBSA National medical policy review. New medically necessary and investigational indications described. New references added. Effective 5/1/2017.
8/2015	BCBSA national medical policy review. Policy title changed from “Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients With Chronic Liver Disease” to “Non-Invasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease.” New investigational indications described. Clarified coding information. Effective 8/1/2015.
9/2014	New references added from BCBSA National medical policy.
10/2013	New references from BCBSA National medical policy.
3/2013	New policy describing non-coverage. Effective 3/1/2013.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Siemens Healthineers. Press Releases: FDA Grants Breakthrough Device Designation to Siemens Healthineers Enhanced Liver Fibrosis Test. November 8, 2018. https://www.siemens-healthineers.com/en-us/press-room/press-releases/elftest.html. Accessed October 7, 2019.
2. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. Oct 2002;97(10):2614-2618. PMID 12385448.
3. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology. Mar 2009;49(3):1017-1044. PMID 19243014.
4. Mehta SH, Lau B, Afdhal NH, et al. Exceeding the limits of liver histology markers. J Hepatol. Jan 2009;50(1):36-41. PMID 19012989.
5. Trikalinos TA, Balion CM. Chapter 9: options for summarizing medical test performance in the absence of a gold standard. J Gen Intern Med. Jun 2012;27(Suppl 1):S67-75. PMID 22648677.
6. Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess. Jan 2015;19(9):1-409, v-vi. PMID 25633908.

7. Houot M, Ngo Y, Munteanu M, et al. Systematic review with meta-analysis: direct comparisons of biomarkers for the diagnosis of fibrosis in chronic hepatitis C and B. Aliment Pharmacol Ther. Jan 2016;43(1):16-29. PMID 26516104.
8. Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet. Apr 7 2001;357(9262):1069-1075. PMID 11297957.
9. Poynard T, McHutchison J, Manns M, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. Hepatology. Aug 2003;38(2):481-492. PMID 12883493.
10. Poynard T, Munteanu M, Imbert-Bismut F, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chem. Aug 2004;50(8):1344-1355. PMID 15192028.
11. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol. Jun 2004;99(6):1160-1174. PMID 15180741.
12. Lichtinghagen R, Bahr MJ. Noninvasive diagnosis of fibrosis in chronic liver disease. Expert Rev Mol Diagn. Sep 2004;4(5):715-726. PMID 15347264.
13. Rossi E, Adams L, Prins A, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. Clin Chem. Mar 2003;49(3):450-454. PMID 12600957.
14. Poynard T, de Ledinghen V, Zarski JP, et al. Relative performances of FibroTest, Fibroscan, and biopsy for the assessment of the stage of liver fibrosis in patients with chronic hepatitis C: a step toward the truth in the absence of a gold standard. J Hepatol. Mar 2012;56(3):541-548. PMID 21889468.
15. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. Apr 17 2014;370(16):1483-1493. PMID 24725238.
16. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. May 15 2014;370(20):1889-1898. PMID 24725239.
17. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. Dec 31 2015;373(27):2618-2628. PMID 26569658.
18. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. Dec 31 2015;373(27):2608-2617. PMID 26575258.
19. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. May 15 2014;370(20):1879-1888. PMID 24720702.
20. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. May 22 2014;370(21):1993-2001. PMID 24795201.
21. Naveau S, Raynard B, Ratziu V, et al. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. Clin Gastroenterol Hepatol. Feb 2005;3(2):167-174. PMID 15704051.
22. Ratziu V, Massard J, Charlotte F, et al. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol. 2006;6:6. PMID 16503961.
23. Lassailly G, Caiazzo R, Hollebecque A, et al. Validation of noninvasive biomarkers (FibroTest, SteatoTest, and NashTest) for prediction of liver injury in patients with morbid obesity. Eur J Gastroenterol Hepatol. Jun 2011;23(6):499-506. PMID 21499110.
24. Mohamadnejad M, Montazeri G, Fazlollahi A, et al. Noninvasive markers of liver fibrosis and inflammation in chronic hepatitis B-virus related liver disease. Am J Gastroenterol. Nov 2006;101(11):2537-2545. PMID 17029616.
25. Zeng MD, Lu LG, Mao YM, et al. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. Hepatology. Dec 2005;42(6):1437-1445. PMID 16317674.
26. Park MS, Kim BK, Cheong JY, et al. Discordance between liver biopsy and FibroTest in assessing liver fibrosis in chronic hepatitis B. PLoS One. Feb 2013;8(2):e55759. PMID 23405210.
27. Salkic NN, Jovanovic P, Hauser G, et al. FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: a meta-analysis. Am J Gastroenterol. Jun 2014;109(6):796-809. PMID 24535095.
28. Xu XY, Kong H, Song RX, et al. The effectiveness of noninvasive biomarkers to predict hepatitis B-related significant fibrosis and cirrhosis: a systematic review and meta-analysis of diagnostic test accuracy. PLoS One. Jun 25 2014;9(6):e100182. PMID 24964038.

29. Wai CT, Cheng CL, Wee A, et al. Non-invasive models for predicting histology in patients with chronic hepatitis B. Liver Int. Aug 2006;26(6):666-672. PMID 16842322.
30. Patel K, Gordon SC, Jacobson I, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. J Hepatol. Dec 2004;41(6):935-942. PMID 15582126.
31. Christensen C, Bruden D, Livingston S, et al. Diagnostic accuracy of a fibrosis serum panel (FIBROSpect II) compared with Knodell and Ishak liver biopsy scores in chronic hepatitis C patients. J Viral Hepat. Oct 2006;13(10):652-658. PMID 16970596.
32. Mehta P, Ploutz-Snyder R, Nandi J, et al. Diagnostic accuracy of serum hyaluronic acid, FIBROSpect II, and YKL-40 for discriminating fibrosis stages in chronic hepatitis C. Am J Gastroenterol. Apr 2008;103(4):928-936. PMID 18371145.
33. Patel K, Nelson DR, Rockey DC, et al. Correlation of FIBROSpect II with histologic and morphometric evaluation of liver fibrosis in chronic hepatitis C. Clin Gastroenterol Hepatol. Feb 2008;6(2):242-247. PMID 18187364.
34. Snyder N, Nguyen A, Gajula L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. Clin Chim Acta. Jun 2007;381(2):119-123. PMID 17442291.
35. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. Aug 2003;38(2):518-526. PMID 12883497.
36. Giannini EG, Zaman A, Ceppa P, et al. A simple approach to noninvasively identifying significant fibrosis in chronic hepatitis C patients in clinical practice. J Clin Gastroenterol. Jul 2006;40(6):521-527. PMID 16825935.
37. Bourliere M, Penaranda G, Renou C, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. J Viral Hepat. Oct 2006;13(10):659-670. PMID 16970597.
38. Zarski JP, Sturm N, Guechot J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. J Hepatol. Jan 2012;56(1):55-62. PMID 21781944.
39. Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology. Jun 2009;49(6):1821-1827. PMID 19291784.
40. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology. Jan 2012;55(1):58-67. PMID 21898504.
41. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology. Dec 2004;127(6):1704-1713. PMID 15578508.
42. Siemens Healthineers. Liver Fibrosis Assays: Enhanced Liver Fibrosis (ELF) Test. 2019. https://www.siemens-healthineers.com/laboratory-diagnostics/assays-by-diseases-conditions/liver-disease/elf-test. Accessed October 7, 2019.
43. Sterling RK, Lissen E, Clumeck N et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology, 2006 May 27;43(6). PMID 16729309.
44. Vallet-Pichard A, Mallet V, Nalpas B et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology, 2007 Jun 15;46(1). PMID 17567829.
45. Angulo P, Bugianesi E, Bjornsson ES et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology, 2013 Jul 19;145(4). PMID 23860502.
46. Sanyal AJ, Harrison SA, Ratziu V et al. The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials. Hepatology, 2019 Apr 18. PMID 30993748.
47. National Institute for Health and Care Excellence (NICE). Non-alcoholic fatty liver disease (NAFLD): assessment and management [NG49]. 2016; https://www.nice.org.uk/guidance/ng49. Accessed October 7, 2019.
48. Brener S. Transient elastography for assessment of liver fibrosis and steatosis: an evidence-based analysis. Ont Health Technol Assess Ser. Dec 2015;15(18):1-45. PMID 26664664.

49. Bota S, Herkner H, Sporea I, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int. Sep 2013;33(8):1138-1147. PMID 23859217.
50. Chon YE, Choi EH, Song KJ, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One. Oct 2012;7(9):e44930. PMID 23049764.
51. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. Apr 2008;134(4):960-974. PMID 18395077.
52. Kwok R, Tse YK, Wong GL, et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther. Feb 2014;39(3):254-269. PMID 24308774.
53. Poynard T, Morra R, Ingiliz P, et al. Assessment of liver fibrosis: noninvasive means. Saudi J Gastroenterol. Oct 2008;14(4):163-173. PMID 19568532.
54. Poynard T, Ngo Y, Munteanu M, et al. Noninvasive markers of hepatic fibrosis in chronic hepatitis B. Curr Hepat Rep. Jun 2011;10(2):87-97. PMID 21654911.
55. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol. Nov 2007;102(11):2589-2600. PMID 17850410.
56. Shi KQ, Tang JZ, Zhu XL, et al. Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy. J Gastroenterol Hepatol. Jun 2014;29(6):1149-1158. PMID 24476011.
57. Steadman R, Myers RP, Leggett L, et al. A health technology assessment of transient elastography in adult liver disease. Can J Gastroenterol. Mar 2013;27(3):149-158. PMID 23516679.
58. Stebbing J, Farouk L, Panos G, et al. A meta-analysis of transient elastography for the detection of hepatic fibrosis. J Clin Gastroenterol. Mar 2010;44(3):214-219. PMID 19745758.
59. Talwalkar JA, Kurtz DM, Schoenleber SJ, et al. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol. Oct 2007;5(10):1214-1220. PMID 17916549.
60. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol. Apr 2011;54(4):650-659. PMID 21146892.
61. Tsochatzis EA, Crossan C, Longworth L, et al. Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis C. Hepatology. Sep 2014;60(3):832-843. PMID 25043847.
62. Friedrich-Rust M, Nierhoff J, Lupsor M, et al. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. J Viral Hepat. Feb 2012;19(2):e212-219. PMID 22239521.
63. Geng XX, Huang RG, Lin JM, et al. Transient elastography in clinical detection of liver cirrhosis: A systematic review and meta-analysis. Saudi J Gastroenterol. Jul-Aug 2016;22(4):294-303. PMID 27488324.
64. Jiang W, Huang S, Teng H, et al. Diagnostic accuracy of point shear wave elastography and transient elastography for staging hepatic fibrosis in patients with non-alcoholic fatty liver disease: a meta-analysis. BMJ Open. Aug 23 2018;8(8):e021787. PMID 30139901.
65. Li Y, Huang YS, Wang ZZ, et al. Systematic review with meta-analysis: the diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. Aliment Pharmacol Ther. Feb 2016;43(4):458-469. PMID 26669632.
66. Njei B, McCarty TR, Luk J, et al. Use of transient elastography in patients with HIV-HCV coinfection: A systematic review and meta-analysis. J Gastroenterol Hepatol. Oct 2016;31(10):1684-1693. PMID 26952020.
67. Pavlov CS, Casazza G, Nikolova D, et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. Cochrane Database Syst Rev. Jan 22 2015;1:CD010542. PMID 25612182.
68. Xu X, Su Y, Song R, et al. Performance of transient elastography assessing fibrosis of single hepatitis B virus infection: a systematic review and meta-analysis of a diagnostic test. Hepatol Int. Oct 2015;9(4):558-566. PMID 26187292.

69. Abdel Alem S, Elsharkawy A, El Akel W et al. Liver stiffness measurements and FIB-4 are predictors of response to sofosbuvir-based treatment regimens in 7256 chronic HCV patients. Expert Rev Gastroenterol Hepatol, 2019 Aug 17;1-8:1-8. PMID 31418303.
70. Guo Y, Parthasarathy S, Goyal P, et al. Magnetic resonance elastography and acoustic radiation force impulse for staging hepatic fibrosis: a meta-analysis. Abdom Imaging. Apr 2015;40(4):818-834. PMID 24711064.
71. Hu X, Qiu L, Liu D, et al. Acoustic Radiation Force Impulse (ARFI) Elastography for noninvasive evaluation of hepatic fibrosis in chronic hepatitis B and C patients: a systematic review and meta-analysis. Med Ultrason. Jan 31 2017;19(1):23-31. PMID 28180193.
72. Liu H, Fu J, Hong R, et al. Acoustic radiation force impulse elastography for the non-invasive evaluation of hepatic fibrosis in non-alcoholic fatty liver disease patients: a systematic review & meta-analysis. PLoS One. Jul 2015;10(7):e0127782. PMID 26131717.
73. Nierhoff J, Chavez Ortiz AA, Herrmann E, et al. The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. Eur Radiol. Nov 2013;23(11):3040-3053. PMID 23801420.
74. Singh S, Venkatesh SK, Wang Z, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. Clin Gastroenterol Hepatol. Mar 2015;13(3):440-451 e446. PMID 25305349.
75. Singh S, Venkatesh SK, Loomba R, et al. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. Eur Radiol. May 2016;26(5):1431-1440. PMID 26314479.
76. Xiao G, Zhu S, Xiao X et al. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology, 2017 Jun 7;66(5). PMID 28586172.
77. Kobayashi K, Nakao H, Nishiyama T, et al. Diagnostic accuracy of real-time tissue elastography for the staging of liver fibrosis: a meta-analysis. Eur Radiol. Jan 2015;25(1):230-238. PMID 25149296.
78. Hong H, Li J, Jin Y, et al. Performance of real-time elastography for the staging of hepatic fibrosis: a meta-analysis. PLoS One. Dec 2014;9(12):e115702. PMID 25541695.
79. Singh S, Muir AJ, Dieterich DT, et al. American Gastroenterological Association Institute Technical Review on the role of elastography in chronic liver diseases. Gastroenterology. May 2017;152(6):1544-1577. PMID 28442120.
80. National Institute for Health and Care Excellence (NICE). Hepatitis B (chronic): diagnosis and management [CG165]. 2013; https://www.nice.org.uk/guidance/cg165. Accessed October 7, 2019.
81. American Association for the Study of Liver Diseases, Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. 2018; https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_May_24_2018b.pdf. Accessed October 7, 2019.
82. Horowitz JM, Kamel IR, Arif-Tiwari H, et al. ACR Appropriateness Criteria(R) Chronic Liver Disease. J Am Coll Radiol. May 2017;14(5s):S103-s117. PMID 28473066.
83. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. Jul 2015;63(1):237-264. PMID 25911335.