# FEP 2.04.41 Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease

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**Related Policies:** None

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

## Description

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.

## FDA REGULATORY STATUS

In November 2008, Acuson S2000™ Virtual Touch (Siemens AG, Erlanger, Germany), which provides acoustic radiation force impulse imaging, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K072786).

In August 2009, AIXPLORER® Ultrasound System (SuperSonic Imagine, Aix en Provence, France), which provides shear wave elastography, was cleared for marketing by FDA through the 510(k) process (K091970).

In June 2010, Hitachi HI VISION™ Preirus™ Diagnostic Ultrasound Scantier (Hitachi Medical Systems America, Twinsburg, OH), which provides real-time tissue elastography, was cleared for marketing by FDA through the 510(k) process (K093466).

In April 2013, FibroScan® (EchoSens, Paris, France), which uses transient elastography, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K123806).

In February 2017, ElastQ Imaging shear wave elastography (Royal Phillips, Amsterdam, the Netherlands) was cleared for marketing by FDA through the 510(k) process (K163120).

FDA product code: IYO.

## POLICY STATEMENT

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 magnetic resonance elastography, acoustic radiation force impulse imaging (eg, Acuson S2000), or real-time tissue elastography, is considered **investigational** for the evaluation or monitoring of patients with chronic liver disease.

## POLICY GUIDELINES

Multianalyte assays with algorithmic analyses use the results from multiple assays of various types in an algorithmic analysis to determine and report a numeric score(s) or probability. The results of individual component assays are not reported separately.

## BENEFIT APPLICATION

Both FibroSURE and FIBROSpect are offered exclusively by reference laboratories, where the global charge will reflect the cost of the underlying laboratory analysis, and then, in addition, the charge associated with the use of the proprietary algorithm to analyze the data.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

## RATIONALE

### Summary of Evidence

#### 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). Relevant outcomes are test accuracy and 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 RCTs that 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 multianalyte serum assays for liver function assessment other than FibroSURE, the evidence includes systematic reviews of observational studies.

Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Studies have frequently included varying cutoffs, some of which were standardized and others not validated. 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 (>10,000 patients). Relevant outcomes are test accuracy and 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 RCTs. These RCTs 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. Relevant outcomes are test accuracy and 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.

## SUPPLEMENTAL INFORMATION

### Practice Guidelines and Position Statements

### Nonalcoholic Fatty Liver Disease

#### *American Gastroenterological Association et al*

The 2012 practice guidelines on the diagnosis and management of nonalcoholic fatty liver disease (NAFLD), developed by the American Gastroenterological Association, the American Association for the Study of Liver Diseases, and the American College of Gastroenterology did not reference multianalyte assays with algorithmic analyses for liver fibrosis evaluation and management.[83] The guidelines mentioned that while transient elastography has shown high sensitivity and specificity in identifying advanced fibrosis in patients with NAFLD, the test is not as accurate when used in patients with high body mass index.

### *National Institute for Health and Care Excellence*

In 2016, the National Institute for Health and Care Excellence (NICE) published guidance on the assessment and management of NAFLD.[84] The guidance did not reference elastography or multianalyte assays with algorithmic analyses. The guidance recommended the enhanced liver fibrosis test to test for advanced liver fibrosis.

### *American College of Gastroenterology*

In 2017, the American College of Gastroenterology published guidelines on the role of elastography in chronic liver disease. The guidelines indicated that, in adults with NAFLD, vibration-controlled transient elastography (VCTE) has better diagnostic performance for diagnosing cirrhosis than the aspartate aminotransferase to platelet ratio index and Fibrosis-4 Index (FIB-4) (very low quality of evidence).[85] Moreover, the guidelines stated that, in adults with NAFLD, magnetic resonance–guided elastography has little or no increased diagnostic accuracy for identifying cirrhosis compared with VCTE in patients who have cirrhosis, and has higher diagnostic accuracy than VCTE in patients who do not have cirrhosis (very low quality of evidence).

## Hepatitis B and C Viruses

### *National Institute for Health and Care Excellence*

In 2013, NICE published guidance on the management and treatment of patients with hepatitis B.[86] The guidance recommended offering transient elastography as the initial test in adults diagnosed with chronic hepatitis B, to inform the antiviral treatment decision (see Table 1).

**Table 1. Antiviral Treatment Recommendations by Transient Elasticity Score**

| Transient Elasticity Score | Antiviral Treatment |
|---|---|
| >11 kPa | Offer antiviral treatment |
| 6-10 kPa | Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment |
| <6 kPa plus abnormal (ALT) | Offer liver biopsy to confirm fibrosis level prior to offering antiviral treatment |
| <6 plus normal ALT | Do not offer antiviral treatment |

ALT: alanine aminotransferase.

As of September 2016, NICE had placed a pause on the development of the guidance on hepatitis C, citing instability and costs in the availability of treatments for the condition.

### *American Association for the Study of Liver Diseases and Infectious Diseases Society of America*

The 2016 American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines for testing, managing, and treating hepatitis C virus (HCV) recommended that, for counseling and pretreatment assessment purposes, the following should be completed:[87]

> "Evaluation for advanced fibrosis, using liver biopsy, imaging, or noninvasive markers, is recommended in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening).
> Rating: Class I, Level A [evidence and/or general agreement; data derived from multiple randomized trials, or meta-analyses]"

The guidelines noted that there are several noninvasive tests to stage the degree of fibrosis in patients with hepatitis C. Tests included indirect serum biomarkers, direct serum biomarkers, and vibration-controlled liver elastography. The guidelines assert that no single method is recognized to have high accuracy alone and careful interpretation of these tests is required.

### *American College of Gastroenterology*

Guidelines published by the American College of Gastroenterology in 2017 on the role of elastography in chronic liver disease indicated that, in adults with chronic hepatitis B virus and HCV, VCTE has better diagnostic performance for diagnosing cirrhosis than the aminotransferase to platelet ratio index and FIB-4 (moderate quality of evidence for HCV, low quality of evidence for hepatitis B virus).[85] In addition, the guidelines stated that, in adults with HCV, magnetic resonance–guided elastography has little or no increased diagnostic accuracy for identifying cirrhosis compared with VCTE in patients who have cirrhosis, and has lower diagnostic accuracy than VCTE in patients who do not have cirrhosis (very low quality of evidence).

## Chronic Liver Disease

### *American College of Radiology*

The 2017 American College of Radiology appropriateness criteria rated 1-dimensional transient elastography as a 7 (usually appropriate) for the diagnosis of liver fibrosis in patients with chronic liver disease.[88] The criteria noted, “This procedure is less reliable in diagnosing liver fibrosis and cirrhosis in patients with obesity or ascites.”

### *European Association for the Study of Liver Disease et al*

The European Association for the Study of Liver Disease and the Asociacion Latinoamericana para el Estudio del Higado convened a panel of experts to develop clinical practice guidelines on the use of noninvasive tests to evaluate liver disease severity and prognosis, with results published in 2015.[89] The publication provided a summary of the advantages and disadvantages of noninvasive techniques (serum biomarkers, imaging techniques). A summary of the joint recommendations for serum biomarkers and transient elastography is provided in Table 2.

**Table 2. Recommendations for Serum Biomarkers and Transient Elastography**

| Biomarkers | QOE | SOR |
|---|---|---|
| “Serum biomarkers can be used in clinical practice due to high applicability (>95%) and good reproducibility.” | High | Strong |
| “TE can be considered the non-invasive standard for the measure of LS” | High | Strong |
| “Serum biomarkers are well-validated for chronic viral hepatitis…. They are less well-validated for NAFLD not validated in other chronic kidney diseases.” | High | Strong |
| "For the diagnosis of significant fibrosis a combination of tests with concordance may provide the highest diagnostic accuracy” | High | Weak |
| “All HCV patients should be screened to exclude cirrhosis by TE [or]… serum biomarkers….” | High | Strong |
| “Non-invasive assessment including serum biomarkers or TE can be used as first line procedure for the identification of patients at low risk of severe fibrosis/cirrhosis” | High | Strong |
| “Follow-up assessment by either serum biomarkers or TE for progression of liver fibrosis should be used for NAFLD patients at a 3 year interval” | Moderate | Strong |

HCV: hepatitis C virus; LS: liver stiffness; NAFLD: nonalcoholic fatty liver disease; QOE: quality of evidence; SOR: strength of recommendation; TE: transient elastography.

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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## POLICY HISTORY

| Date | Action | Description |
|---|---|---|
| December 2013 | New Policy | |

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|---|---|---|
| September 2014 | Update Policy | Policy updated with literature review, reference 22 added. Policy statement unchanged. |
| March 2015 | Update Policy | Policy updated with literature review. Policy statement unchanged. |
| March 2017 | Replace Policy | Policy updated literature review through October 7, 2016; references 1-4, 6- 7, 16--22, 46-49, 64-80, 83, and 85-87 added. Rationale reorganized. Policy statements changed; FibroScan and FibroSURE changed to medically necessary for evaluation of chronic liver disease. |
| March 2018 | Update Policy | Policy updated with literature review through September 11, 2017; references 65, 72, 74, and 85 added. Policy statements unchanged. |