Subject: Non-invasive Tests for Hepatic Fibrosis

Background: Accurately diagnosing liver fibrosis and inflammatory activity are the most important factors for determining the stage of the disease, assessing the patient's prognosis, and predicting treatment responses. Liver biopsy has been the gold standard test for assessing hepatic fibrosis. Recently, non-invasive tests have been developed as alternatives to biopsy.

Policy and Coverage Criteria:
Harvard Pilgrim Health Care (HPHC) considers the following non-invasive tests as reasonable and medically necessary to assess and evaluate the degree of liver fibrosis and cirrhosis in members with chronic liver disease (e.g. chronic Hepatitis C Virus (HCV) infection):

- Imaging tests
  - Ultrasound-based Transient elastography (e.g. FibroScan)
- Serum marker tests: Only one of the below tests is covered only single time (once) per member
  - FibroTest-ActiTest;
  - HCV-FibroSure;

Exclusions: Harvard Pilgrim Health Care (HPHC) considers non-invasive fibrosis test as not medically necessary for all other indications. In addition, HPHC does not cover monitoring of fibrosis or cirrhosis in individuals with chronic liver disease (e.g. chronic Hepatitis C Virus (HCV) infection) for the following:

- Imaging tests
  - Ultrasound-based Transient elastography (e.g. FibroScan)
- Serum marker tests: Only one of the below tests is covered for only single time per member
  - FibroTest-ActiTest;
  - HCV-FibroSure;

In addition, Harvard Pilgrim Health Care (HPHC) considers the following non-invasive fibrosis tests as not medically necessary in the diagnosis (evaluation) and monitoring of individuals with hepatitis C or other chronic liver disease. There is insufficient evidence in clinical literature to support their use (this list is not all-inclusive):

- Imaging tests
  - Acoustic Radiation Force Impulse (ARFI)
  - Magnetic Resonance Elastography (MRE)
  - Real time Shear Wave Elastography (SWE)
- Serum marker tests
  - FibroMAX
  - FibroSpect
  - HepaScore
  - FibroMeter
  - NASH FibroSure
Supporting Information:

Transient elastography (TE) involves the ultrasonographic analysis of wave propagation and tissue deformation in patients suspected of or known to have chronic liver disease. TE is based on the principle that fibrosis changes the elasticity and viscosity of tissue. By assessing the propagation of acoustic waves through liver tissue, the extent of fibrosis can be measured. FibroScan uses vibration-controlled TE to noninvasively measure liver stiffness.

Serologic marker testing for hepatic fibrosis involves indirect and direct markers. Indirect markers reflect alterations in hepatic function, but do not directly reflect extracellular matrix metabolism. Examples include the platelet count, coagulation studies, and liver aminotransferases. Direct markers of fibrosis reflect extracellular matrix turnover. Examples include procollagen types I and III, hyaluronic acid, and tissue inhibitor of metalloproteinase.

Current clinical evidence supports the use of TE for staging of hepatic fibrosis related to liver disease. A number of systematic reviews and meta-analyses reported diagnostic accuracy of TE for fibrosis and cirrhosis assessment. There is limited evidence to support the use of serum marker tests to accurately stage liver fibrosis. Fernandez et al (2015) conducted a retrospective study including 135 patients with alcoholic liver disease who underwent liver biopsy. Fibroscan, Fibrotest, FIB-4, APRI, and Forns’ scores were tested in all patients. Diagnostic accuracy of Fibroscan was 0.89 for the diagnosis of advanced fibrosis and 0.93 for the diagnosis of cirrhosis. Fibroscan performed better than all other tests. The authors concluded that Fibroscan is currently the most reliable noninvasive method for the diagnosis of advanced liver fibrosis and cirrhosis in alcoholic liver disease.

Seo et al (2015) investigated the diagnostic performance of liver stiffness (LS) measurement using TE in Korean patients with chronic hepatitis B and C (CHB and CHC). 916 patients who underwent liver biopsy and TE were analyzed. Aspartate aminotransferase (AST)-to-platelet ratio indexes (APRI) were calculated. TE was significantly superior to APRI in CHB patients and was significantly superior for predicting ≥ F3 stage, whereas it was similar for predicting ≥ F2 and F4 stage in CHC patients. The authors concluded that TE can accurately assess the degree of liver fibrosis and was superior to APRI for predicting each fibrosis stage in Korean patients with CVH. Gobel et al (2015) investigated the diagnostic significance of TE in a daily routine clinical setting in comparison to clinical signs, laboratory parameters and US in 291 patients with chronic liver disease who underwent liver biopsy. Sensitivity of TE for the detection of liver cirrhosis was 90.4% compared to 80.1% for US, 58% for platelet count and 45.1% for cutaneous liver signs. Combining TE with US increased sensitivity to 96.1%. The authors concluded that TE is superior to routine diagnostic tests allowing detection of liver cirrhosis in additional 10-16% of patients with chronic liver disease that would have been missed.

Jia et al (2015) compared liver stiffness results using TE to histological staging and serum fibrosis markers in 469 patients with CHB. The authors found that TE is a reliable noninvasive technique to predict significant liver fibrosis in Chinese patients with CHB and is superior to current biomarker panels. It was also found that enhanced inflammatory activity can lead to elevated stiffness values unrelated to histological fibrosis stage. Castera et al (2014) compared the performance of TE, Fibrotest, APRI, and two algorithms combining TE and Fibrotest or APRI and Fibrotest in 116 HIV/HCV coinfected patients. For a fibrosis score of greater than or equal to 2, both TE and Fibrotest had a significantly better diagnostic performance than APRI. For a fibrosis score of 4, TE had significantly better performance than Fibrotest. The authors concluded that in HIV/HCV-coinfected patients, TE and Fibrotest have a similar diagnostic accuracy for significant fibrosis. For patients with cirrhosis, TE has the best accuracy. The combination algorithms did not improve diagnostic performance.

Aykut et al (2014) compared the diagnostic performance of FibroMeter, NFSA, and TE for the detection of liver fibrosis in 88 patients with biopsy-proven NAFLD. The sensitivities/specificities for the FibroMeter score, NFSA, and TE for the diagnosis of significant fibrosis (F2 + F3 + F4 fibrosis) were 38.6%/86.4%, 52.3%/88.6%, and

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75.0%/93.2%, respectively. The areas under the receiver operating characteristic curves of TE were significantly higher than those of both the FibroMeter score and NFSA. No differences were found between the FibroMeter score and NFSA for the detection of significant and severe fibrosis, although the diagnostic performance of the FibroMeter score was higher than that of the NFSA score for cirrhosis. The authors concluded that TE showed the best diagnostic performance for the noninvasive assessment of liver fibrosis in NAFLD patients.

Abd El Rihim et al. (2013) found Fibroscan and APRI to be clinically useful tests for detecting cirrhosis. The authors performed a systematic review and meta-analysis of diagnostic accuracy studies comparing Fibroscan and APRI with liver biopsy for hepatic fibrosis. 23 studies for fibroscan and 20 studies for APRI in full publication were identified. For patients with stage IV fibrosis (cirrhosis), the pooled estimates for sensitivity of fibroscan were 83.4% and specificity 92.4%. For patients with stage IV fibrosis (cirrhosis), the pooled estimates for sensitivity of APRI at cutoff point of 1.5 were 66.5% and specificity 71.7%.

Adebajo et al (2012) performed a systematic review and meta-analysis of studies comparing US-based TE to live biopsy for the detection of hepatic fibrosis due to recurrent HCV infection after liver transplantation (LT). Six fully published studies were identified for analysis. Among these studies, the pooled estimates were 83% for sensitivity, 83% for specificity, 4.95 for the positive likelihood ratio, 0.17 for the negative likelihood ratio, and 30.5 for the diagnostic odds ratio. For the 5 studies that assessed cirrhosis, the pooled estimates were 98% for sensitivity, 84% for specificity, 7 for the positive likelihood ratio, 0.06 for the negative likelihood ratio, and 130 for the diagnostic odds ratio. A diagnostic threshold the authors concluded that US-based TE has excellent diagnostic accuracy for identifying cirrhosis due to a recurrent HCV infection after LT. The detection of significant fibrosis is more accurate for these patients versus patients whose native liver is chronically infected with HCV.

UptoDate analysis of various studies have found Hepascore to be a useful test for predicting fibrosis in HCV. UptoDate also states that the panels of direct markers of hepatic fibrosis include FibroSpect II, Serum Hyaluronic Acid level with serum AST and Albumin level (SHASTA), and the European Liver Fibrosis panel (ELF). However, none of this are yet part of standard clinical practice. There is a variability on the accuracy of the panels depending on the cut-offs used. For example, in a study on 1021 patients with chronic liver disease ELF was shown to have sensitivity of 87 to 90 percent and a specificity of 41 to 51 percent for diagnosing moderate or severe fibrosis using a threshold score of 0.102, whereas the specificity increased to 95 percent using a threshold score of 0.457.

UptoDate report also states that serum marker tests have their own limitations as they are not specific for liver and their levels are affected by the hepatic clearance rate. They are typically surrogates of liver fibrosis instead of inflammation. Moreover, they typically reflect matrix turnover and hence tend to be more elevated with high inflammatory activity and lower with no inflammation.

According to technology assessment report by ECRI a large body of studies show that Acoustic Radiation Force Impulse (ARFI) is non-inferior to serum markers and transient elastography (TE) for assessing liver fibrosis but is less accurate than magnetic resonance elastography (MRE) or two-dimensional shear-wave elastography (2-D SWE); however, there is insufficient evidence to assess ARFI’s effect on patient outcomes and healthcare costs. Hayes has assigned a rating of C for use of MRE for detecting and staging liver fibrosis in adults with known or suspected liver disease despite high reported AUC due to lack of uniformity in standardized cut-off values for staging of liver fibrosis across the literature. According to Hayes lack of standardization of cut-off for staging limits the generalized application of technology in clinical practice. UptoDate also states that though MRE is comparable to ultrasound-based transient elastography in terms of accuracy, it can be much more expensive than ultrasound.
Fibroscan® (Echosens SA, Paris, France, available in the US through Sandhill Scientific, Highlands Ranch, CO) received FDA 510(k) approval on April 5, 2013. Fibroscan is indicated for noninvasive measurement of shearwave speed at 50 Hz in the liver. The FibroScan® device uses transient elastography for the non-invasive measurement of liver shear wave speed. A mechanical vibrator produces low-amplitude elastic waves that travel through the skin and intercostal space into the liver.

European Association for the Study of the Liver states the 2D-SWE is a promising technique that is currently under investigation. It seems to be at least equivalent to TE and point shear wave elastography (pSWE)/ARFI for non-invasive staging of liver fibrosis in viral hepatitis (B1—Moderate quality of evidence: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, strong recommendation).

Comparison between MR elastography and TE has provided conflicting results. Further data are needed (A1—High quality of evidence: Further research is very unlikely to change our confidence in the estimate of effect, strong recommendation).

**Coding:**

Codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible.

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis [when specified as serum markers for liver fibrosis, including FIBROSpect II, Hepascore combination tests]</td>
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<tr>
<td>83520</td>
<td>Immunoassay, analyte, quantitative; not otherwise specified [If billed for FIBROspect or HCV FIBROSURE FibroMAX, FibroTest, ActiTest, HepaScore]</td>
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<tr>
<td>83883</td>
<td>Nephelometry, each analyte not elsewhere specified [If billed for FIBROspect or HCV FIBROSUREFibroMAX, FibroTest, ActiTest, HepaScore]</td>
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<tr>
<td>91200</td>
<td>Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report</td>
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**Billing Guidelines:**

Member’s medical records must document that services are medically necessary for the care provided. Harvard Pilgrim Health Care maintains the right to audit the services provided to our members, regardless of the participation status of the provider. All documentation must be available to HPHC upon request. Failure to produce the requested information may result in denial or retraction of payment.

**References:**


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Summary of Changes:

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<tr>
<th>Date</th>
<th>Change</th>
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<td>4/18</td>
<td>Updated references and background; criteria revised; CPT and ICD-10 code analysis by external reviewer done. No coding changes made.</td>
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Approved by Medical Policy Review Committee: 4/24/2018
Reviewed/Revised: 5/16, 4/18
Initiated: n/a