Clinical Policy Title: Noninvasive assessment of hepatic fibrosis

Clinical Policy Number: 08.01.03

Effective Date: Oct. 1, 2014
Initial Review Date: June 18, 2014
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Policy contains:
- Chronic hepatitis B and C.
- Transient elastography (FibroScan®).
- Acoustic radiation force impulse (ARFI) imaging.

Related Policies:
CP# 01.01.01   Serum biomarkers for liver fibrosis in persons with hepatitis C

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the use of transient elastography (TE, also called FibroScan®) and acoustic radiation force impulse (ARFI) to be medically necessary when ordered as part of an evaluation of hepatic pathology.

<table>
<thead>
<tr>
<th>Treatment guidance for interpretation of noninvasive assessment of hepatic fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both elastography and ARFI are Food and Drug Administration (FDA)-approved, ultrasound-based techniques for estimating the extent of liver fibrosis. Evidence-based criteria for reproducible results of noninvasive studies indicate:</td>
</tr>
<tr>
<td>• FibroScan® value of &gt; 12.5 kilopascals has been associated with histologic cirrhosis.</td>
</tr>
<tr>
<td>• ARFI value of &gt; 1.75 meters/second has been associated with histologic cirrhosis.</td>
</tr>
<tr>
<td>• The scatter of scores in non-cirrhotic liver disease makes the tests unreliable for correlation with Metavir Stage 3 or lower.</td>
</tr>
</tbody>
</table>

Keystone First considers the use of magnetic resonance imaging (MRI), magnetic resonance elastography (MRE), computed tomography (CT), or hepatic chemistries such as FIBROSpectSM to be investigational and, therefore, not medically necessary.
Limitations:

All other uses of elastography are not medically necessary.

Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:

91200 - Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report

0346T - Add-on code; ultrasound elastography

Alternative covered services:

- Physician office visits.
- Liver biopsy.

Background

Liver fibrosis and chronic cirrhosis represent the pathologic results of chronic liver injury. This may be the result of infection with one of the viral etiologies such as hepatitis B, C, or E or with toxins such as alcohol.

Hepatitis C virus (HCV) is a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The Centers for Disease Control and Prevention (CDC) estimates that 3.2 million people in the United States have hepatitis C infection (Smith 2012). Tice (2014) described the natural history of HCV infection as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Among 100 individuals with HCV (number of individuals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remain asymptomatic</td>
<td>70 – 80</td>
</tr>
<tr>
<td>Develop chronic infection</td>
<td>75 – 85</td>
</tr>
<tr>
<td>Develop chronic liver disease</td>
<td>60 – 70</td>
</tr>
<tr>
<td>Develop symptoms</td>
<td>20 – 30</td>
</tr>
<tr>
<td>Develop cirrhosis over 20 to 30 years</td>
<td>5 – 20</td>
</tr>
<tr>
<td>Die from cirrhosis or liver cancers</td>
<td>1 – 5</td>
</tr>
</tbody>
</table>

The increased surveillance with the advent of effective oral therapies for HCV now makes this disease a major public health effort. In 2013, the United States Preventive Services Task Force recommended screening of adults born between 1945 and 1965 (Moyer 2013). Because the majority of infected patients are asymptomatic and have low risk of disease progression, current treatment recommendations focus on proper patient selection, including those with advanced fibrosis or cirrhosis (i.e., Metavir Stage 3 or 4).
Currently, liver biopsy is the gold standard for diagnosis of the stage of hepatic pathology but is associated with complications ranging from pain to perforation of internal organs. The American Association for the Study of Liver Diseases (AASLD) reports mortality in up to one in 10,000 liver biopsies (Rockey 2009). Additionally, sampling errors may provide misinformation for care.

There are several noninvasive alternatives to liver biopsy, and most are rapidly evolving. However, most do not have sufficient correlation with biopsy results to warrant making treatment decisions based on these alone. Over the course of time, recommendations from specialty societies generated by evidence-based literature may change.

In 2012, FDA granted 510(k) approval for use of FibroScan® as a commercially available TE unit, citing the high degree of reliability of measurement. The technology is based on the noninvasive 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. Ultrasound is used to track the shear wave and to measure its speed, which is correlated with the elasticity of the liver.

**Searches**

Keystone First searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

Search terms were: "Elasticity Imaging Techniques" (MeSH), “noninvasive liver,” “imaging liver” and “noninvasive hepatitis C.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Wilder (2014) and Foucher (2006) illustrate the importance of both the etiology of hepatic fibrosis and cirrhosis and differences in optimal elastography cutoffs used to define the stage of liver fibrosis on interpretation of test results. Wilder (2014) pointed to the high degree of accuracy by FibroScan® for patients with cirrhosis but also a higher error rate at stages Metavir F2 or less. A compilation of reviews by Wilder (2014) and Foucher (2006) found the following diagnostic characteristics for FibroScan®:
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Advanced</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>fibrosis,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metavir ≥ F2</td>
<td></td>
<td></td>
<td>Metavir ≥ F4</td>
</tr>
<tr>
<td></td>
<td>cutoff (kPa)</td>
<td></td>
<td></td>
<td>cutoff (kPa)</td>
</tr>
<tr>
<td>HBV</td>
<td>≥7.2</td>
<td>0.74</td>
<td>0.88</td>
<td>≥11</td>
</tr>
<tr>
<td>HCV</td>
<td>≥7.1</td>
<td>0.68</td>
<td>0.89</td>
<td>≥12.5</td>
</tr>
<tr>
<td>HCV + HIV</td>
<td>7.2</td>
<td>0.88</td>
<td>0.66</td>
<td>14.6</td>
</tr>
<tr>
<td>Nonalcoholic steatohepatitis</td>
<td>7</td>
<td>0.76</td>
<td>0.80</td>
<td>10.5</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>8.8</td>
<td>0.67</td>
<td>1.00</td>
<td>16.9</td>
</tr>
<tr>
<td>Alcoholic liver disease (from</td>
<td>7.2</td>
<td>0.64</td>
<td>0.85</td>
<td>17.6</td>
</tr>
<tr>
<td>Foucher)</td>
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</tbody>
</table>

**Policy updates:**

Crossan (2015) reviewed the cost-effectiveness of treating patients in the absence of liver biopsy using a variety of statistical models and generally found FibroScan® to be the most cost-effective test. According to Moroşan (2014), liver biopsy provided the most valid information to avoid subjecting patients to inappropriate medication should they have mild disease.

In 2016, we identified four new systematic reviews and meta-analyses (Houot, 2016; Li, 2016; Liu, 2015; Singh, 2015), one systematic review update (Hayes, 2014 [updated 2015]) and two guideline updates (AASLD and Infectious Disease Society of America [IDSA], 2016, Terrault 2016) for this policy. The systematic reviews and meta-analyses confirmed earlier findings that noninvasive tests, such as FibroScan® or ARFI, may be useful in ruling out cirrhosis, but are less accurate in predicting presence of significant fibrosis (F2 or higher) across a range of etiologies. Current guidelines recommend that all persons with HCV or HBV infection undergo an evaluation for advanced fibrosis using liver biopsy or noninvasive techniques to facilitate an appropriate decision regarding treatment strategy and management of cirrhosis (AASLD and IDSA 2016, Terrault 2016). While none of the noninvasive tests is as diagnostic as liver biopsy, TE is a reliable and easily repeated tool for following the progression of liver fibrosis toward cirrhosis.

Insufficient, low-quality evidence supports MRE for measuring liver stiffness as a surrogate marker of liver disease and fibrosis; the evidence suggests moderate diagnostic performance that improves with disease severity, but prospective studies are needed to confirm these findings before wide application (Singh 2015). These new findings would not alter the conclusions of the initial policy; therefore, no policy changes are warranted.

**Summary of clinical evidence:**
<table>
<thead>
<tr>
<th>Citation</th>
<th>Comments, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houot (2016)</td>
<td>Key points:&lt;br&gt;• Systematic review and Bayesian analyses of 71 studies comprising 185 direct comparisons of test performance based on area under the receiver operating characteristic (AUROC) curves: 99 studies (12,725 patients with advanced fibrosis) and 86 studies (10,929 patients with cirrhosis); 77 groups according to etiology (HCV, HBV, or mixed).&lt;br&gt;• Overall study quality: good (6%), fair (74%), and poor (20%).&lt;br&gt;• In chronic HCV and HBV infection, APRI had lower test performances than FIB-4, FibroScan®, and FibroTest. Lower test performance with FibroScan® than FibroTest for identifying advanced fibrosis in all etiologies, but no significant difference for identifying cirrhosis across all groups.</td>
</tr>
<tr>
<td>Li (2016)</td>
<td>Key points:&lt;br&gt;• Meta-analysis of 27 studies (4,386 total patients) based on fibrosis stage.&lt;br&gt;• F ≥ 2: Sensitivity (Se) = 81%; specificity (Sp) = 82%; summary ROC curve = 0.88 (95% CI 0.85 to 0.91).&lt;br&gt;• F≥ 3: Se = 82%; Sp = 87%; ROC =0.91 (95% CI, 0.88 to 0.93).&lt;br&gt;• F=4: Se = 86%; Sp = 88%; ROC = 0.93 (95% CI, 0.91 to 0.95).&lt;br&gt;• Patient age contributed to heterogeneity.</td>
</tr>
<tr>
<td>Crossan (2015)</td>
<td>Key points:&lt;br&gt;• Meta-analysis and cost effectiveness analysis from the UK perspective.&lt;br&gt;• A majority of tests had only one study from which diagnostic accuracy was derived and lack validated cut-offs for diagnosis of specific fibrosis stages; therefore, there is a high risk of bias.&lt;br&gt;• Further evidence of treatment effectiveness needed for alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD).&lt;br&gt;• Treating everyone without NILTs is cost effective for patients with HCV who are hepatitis B e antigen negative if the higher cost-effectiveness threshold (£30,000) is appropriate. If hepatitis B e antigen positive, two NILTs applied sequentially were cost-effective at the threshold (£20,000) but highly uncertain.</td>
</tr>
<tr>
<td>Hayes (2014, updated 2015)</td>
<td>Key points:&lt;br&gt;• Systematic review of 15 prospective cross-sectional, two cohort studies, and two meta-analyses. All studies had &gt; 200 patients.&lt;br&gt;• Overall quality: Moderate. Limited by lack of standardization of test cutoffs used to determine degrees of fibrosis.&lt;br&gt;• All studies provided some measure of the accuracy of TE for detecting fibrosis ≥ one stage of fibrosis compared with liver biopsy, primarily based on AUROC and to a lesser extent simple accuracy measures.&lt;br&gt;• Preferential patient selection for those with body mass index (BMI) &lt; 30 kg/m².</td>
</tr>
<tr>
<td>Liu (2015)</td>
<td>Key points:&lt;br&gt;• Systematic review and meta-analysis of seven studies (723 total patients with fibrosis stage F2 – F4).&lt;br&gt;• Modest test performance: Se 80%, sp 85%, area under the summary ROC curve (AUC) 0.896 (standard error [SE] 0.031; Q² index 0.830 [SE: 0.033]).&lt;br&gt;• Head to head comparison of ARFI and other elastographic imaging is needed.</td>
</tr>
<tr>
<td>Singh (2015)</td>
<td>Key points:&lt;br&gt;• Systematic review and meta-analysis of 12 retrospective studies (697 total patients) with fibrosis stage 0 (19.5%), stage 1 (19.4%), stage 2 (15.5%), stage 3 (15.9%), and stage 4 (19.7%). The summary AUROC of all fibrosis stages combined was 0.874 (95% CI, 0.844 to 0.896).&lt;br&gt;• Head to head comparison of ARFI and other elastographic imaging techniques is needed.</td>
</tr>
</tbody>
</table>
### Citation | Comments, Methods, Recommendations
--- | ---
| | stage 4 (29.7%).
| | - Mean AUROC (95% CI) by stage:
| | o Any (≥ stage 1), 0.84 (0.76 to 0.92).
| | o Significant (≥ stage 2), 0.88 (0.84 to 0.91).
| | o Advanced fibrosis (≥ stage 3), 0.93 (0.90 to 0.95).
| | o Cirrhosis, 0.92 (0.90 to 0.94).
| | - Overall failure rate = 4.3%. Results are independent of BMI and etiology.
| | - Prospective studies needed to better understand the diagnostic performance of MRE.

| Department of Veterans Affairs (2014) | Key points:
--- | ---
| | - Both elastography and ARFI are FDA-approved, ultrasound-based techniques for estimating the extent of liver fibrosis.
| | - FibroScan® value of > 12.5 kilopascals has been associated with histologic cirrhosis.
| | - ARFI value of > 1.75 meters/second has been associated with histologic cirrhosis.

| Moroşan (2014) | Key points:
--- | ---
| Liver biopsy versus FibroScan® | - Retrospective (?) study of 185 patients serologically diagnosed with chronic hepatitis. (183 patients with HCV, two patients with HBV and HCV).
| | - Strongest correlation between tests was in F0 – F1 and F4 stages.
| | - FibroScan® is able to distinguish patients with minimal or no fibrosis from patients with extensive fibrosis.
| | - Liver biopsy still remains valuable for offering reliable measure of liver changes, as it is regarded more of a selective than routine technique.

| Gara (2013) | Key points:
--- | ---
| Liver biopsy, TE and APRI | - Retrospective study of 109 patients with chronic HCV who underwent TE within six months of liver biopsy at the National Institutes of Health from 2006 to 2011. Fibrosis was scored using the Ishak scale (0 – 6).
| | - TE was in agreement with liver biopsy assessment of fibrosis in 99 patients (91%), whereas APRI was in agreement in only 84 patients (77%).

| Nierhoff (2013) | Key points:
--- | ---
| ARFI imaging | - Meta-analysis of 36 studies (3,951 total patients).
| | - Review shows good diagnostic accuracy of ARFI imaging for the staging of F ≥ 2 and F ≥ 3, and excellent diagnostic accuracy for F = 4.

| Singh (2013) | Key points:
--- | ---
| Association between liver stiffness measurement and outcomes of patients with chronic liver disease | - Meta-analysis from 17 studies (7,058 patients with chronic liver disease).
| | - Baseline liver stiffness measurement (elastography) was highly associated with risk of decompensation, death, and of HCC with 95% confidence.
| | - Significant heterogeneity of results in terms of magnitude but not direction.
| | - Objective markers of hepatic synthetic function that accurately predict an individual’s risk of transitioning to a decompensated state are lacking.

### Glossary

**Acoustic radiation force impulse (ARFI)** — A form of elastography that pushes a beam of ultrasound waves into the soft tissue to measure its stiffness.

**Hepatitis C (HCV)** — Viral infection of the liver caused by the hepatitis C virus that is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma.
Magnetic resonance elastography (MRE) — A new application of MRI that measures hepatic “stiffness” as a surrogate for fibrosis by tracking mechanical waves through the liver. This is an investigational technique.

Sustained viral response (SVR) — The absence of detectable viral elements at 12 weeks post-treatment.

Transient elastography — An ultrasound technology measuring the elastic properties of soft tissues, such as liver. In the case of liver disease, a special probe on an ultrasound imaging device measures the shear wave amplitude and speed as a correlation with liver fibrosis.

References

Professional organizations:


Peer reviewed references:


Clinical trials:

Searched ClinicalTrials.gov on July 19, 2016 using terms: "liver fibrosis" | Open Studies | United States. Thirty-nine studies found, seven relevant.


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

Add-on code 0346T listed as a non-covered service in the following LCDs:


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>91200</td>
<td>Liver elastography, mechanically induced shear wave (eg, vibration, without imaging with interpretation and report)</td>
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<tr>
<td>0346T</td>
<td>Add-on code; ultrasound elastography</td>
<td></td>
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<tr>
<td>ICD-9 Code</td>
<td>Description</td>
<td>Comment</td>
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<tr>
<td>-----------</td>
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<tr>
<td>070.41</td>
<td>Acute hepatitis C with hepatic coma</td>
<td></td>
</tr>
<tr>
<td>070.44</td>
<td>Chronic hepatitis C with hepatic coma</td>
<td></td>
</tr>
<tr>
<td>070.51</td>
<td>Chronic hepatitis C without mention of hepatic coma</td>
<td></td>
</tr>
<tr>
<td>070.54</td>
<td>Chronic hepatitis C without hepatic coma</td>
<td></td>
</tr>
<tr>
<td>070.70</td>
<td>Unspecified hepatitis C without coma</td>
<td></td>
</tr>
<tr>
<td>070.71</td>
<td>Unspecified hepatitis C with coma</td>
<td></td>
</tr>
<tr>
<td>571.5</td>
<td>Cirrhosis of the liver without mention of alcohol</td>
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<table>
<thead>
<tr>
<th>HCPCS Level II</th>
<th>Description</th>
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<tbody>
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