

Noninvasive Assessment of Liver Fibrosis in Chronic Hepatitis C

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Disclaimer

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options may provide coverage under the medical surgical benefits of the Company's Medicaid and Medicare products for medically necessary diagnostic measures for liver disease. Diagnostic measures include liver biopsy, noninvasive markers (e.g., FibroScan) and serological markers.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Highmark Health Options (HHO) – Managed care organization serving vulnerable populations that have complex needs and qualify for Medicaid. Highmark Health Options members include individuals and families with low income, expecting mothers, children, and people with disabilities. Members pay nothing to very little for their health coverage. Highmark Health Options currently services Delaware Medicaid: Delaware Healthy Children Program (DHCP) and Diamond State Health Plan Plus LTSS (DSHP Plus LTSS) members.

POLICY POSITION

1. The following diagnostic testing are considered medically necessary:
 - A. Liver Biopsy
 - B. Radiologic Testing
 - 1) FibroScan
 - 2) Acoustic Radiation Force Impulse (ARFI)

The following medical necessity criteria must be met for radiologic testing:

- a. The patient has a suspected diagnosis of Hepatitis C virus and is a candidate for treatment; AND
 - b. Testing is being performed in order to distinguish hepatic cirrhosis from non-hepatic cirrhosis in persons with hepatitis C; AND
 - c. Is only performed every six months; AND
 - d. Cannot be performed within six months following a liver biopsy; AND
 - e. For the patient that is actively using alcohol or IV drugs, or has a history of abuse, there is documentation by the prescriber regarding the risks of alcohol or IV drug abuse and an offer of referral for substance abuse disorder treatment.
 - f. The patient must have a BMI less than 30 kilograms per square meter (kg/m²) **Note:** Requests for FibroScan in the morbidly obese patient may be reviewed for individual consideration by a Medical Director.
- C. Multi-Analyte Serological Testing
- 1) FibroSure, FibroTest-ActiTest, FIBROSpect
 - 2) HepaScore
 - 3) APRI
2. Contraindications for imaging services
- A. Morbid obesity (equal to or greater than BMI of 30)
Note: Requests for FibroScan in the morbidly obese patient may be reviewed for individual consideration by a Medical Director; OR
 - B. Ascites; OR
 - C. Pregnancy-per the manufacturer; OR
 - D. Presence of pacemaker-per the manufacturer; OR
 - E. Elevated alkaline phosphatase; OR
3. When services are not covered
For conditions and services other than those listed above as the scientific evidence has not been established. Services are considered not medically necessary.
4. Post-payment Audit Statement
The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.
5. Place of Service
The place of service for all diagnostic measurements listed is outpatient.

GOVERNING BODIES APPROVAL

On April 5th, 2013, the FDA provided 510(k) clearance for the FibroScan® device as a commercially available transient elastography unit citing the high degree of reliability of measurement. FibroScan® is indicated for noninvasive measurement of shear wave speed at 50 Hz in the liver. The shear wave speed may be used as an aid to clinical management of patients with liver disease.

No local or National Medicare Determinations were located

Covered Procedure Code(s)

91200	Liver elastography, mechanically induced shear wave (e.g., vibration), without imaging, with interpretation and report.
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Covered Diagnosis Code(s)

B18.2	B19.20	B19.21	K74.0	K74.60
K74.69	Z20.5	Z22.50	Z68.20	Z68.21
Z68.22	Z68.23	Z68.24	Z68.25	Z68.26
Z68.27	Z68.28	Z68.29		

SUMMARY OF LITERATURE

Chronic hepatitis C is one of the more serious types of hepatitis that is spread through exposure to infected blood. The most common form of transmission occurs from sharing needles and less often, sexual contact with an HIV-infected partner, among persons who receive tattoos in unregulated settings, and among infants born to HCV-infected mothers. Other modes of transmission include contaminated medical products during transfusion or other medical procedures. In the United States, the World Health Organization has estimated that there are 3.2 million people living with chronic hepatitis C. The Centers for Disease Control and Prevention (2016) reported that the number of acute hepatitis C virus (HCV) infections increased 3.5-fold from 2010 through 2016 (from 850 to 2,967 reported cases), rising annually throughout this period.

One of the outcomes of chronic hepatitis C is the development of hepatic fibrosis that eventually leads to cirrhosis, liver failure and hepatocellular carcinoma. It has been reported that of those people with chronic hepatitis C, approximately 15 - 25% will require liver transplant. With these statistics, it is essential that patients with chronic hepatitis C be diagnosed and monitored for liver fibrosis. In chronic hepatitis C, quantification of the degree of liver fibrosis is important for prognosis and for treatment.

For some time, liver biopsy has been considered the gold standard for the evaluation of hepatic fibrosis and for initiating treatment (Castera and Bedossa, 2011). A liver biopsy has recognized limitations including sampling error and interobserver variability (Cohen and Afdhal, 2010). Due to limitations of liver biopsy, noninvasive diagnostic tools and procedures have been developed to measure liver fibrosis, monitor its progression and potential response to therapy. These measures include and are not limited to transient elastography (FibroScan), magnetic resonance elastography, and several serum biomarkers.

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 speed, which is then correlated with the elasticity of the liver. FibroScan can be expanded by sampling in different intercostal spaces.

The United States Preventive Services Task Force (USPSTF) suggests that noninvasive tests with good diagnostic accuracy are possible alternatives to liver biopsy for the diagnosis of fibrosis or cirrhosis and was given a Grade B recommendation (Moyer, 2014). In 2014, the VA published a clinical guideline regarding treatment considerations for chronic hepatitis C infection. The guideline authors indicate that although liver biopsy is currently considered the best method for staging fibrosis and grading inflammation, alternatives, such as non-invasive imaging and use of fibrosis markers, may be considered instead of a biopsy, with a cautious understanding of their inherent limitations. Castera et al (2015) reported that liver biopsy is now considered an imperfect gold standard and the procedure should be part of an integrated system with noninvasive testing and serum biomarkers.

Transient elastography (TE, FibroScan) is a novel non-invasive method that has been proposed for the assessment of hepatic fibrosis in patients with chronic liver diseases, by measuring liver stiffness. TE measures the velocity of a low-frequency elastic shear wave propagating through the liver. The wave velocity is indicative of tissue stiffness. The more stiff the tissue the faster the shear wave propagates. TE is a rapid and user-friendly technique that can be easily performed at the bedside or in the outpatient clinic with

immediate results and good reproducibility. Limitations include failure in around 5% of cases, mainly in obese patients. So far, TE has been mostly validated in chronic hepatitis C, with diagnostic performance equivalent to that of serum markers for the diagnosis of significant fibrosis. Combining TE with serum markers increases diagnostic accuracy and as a result, liver biopsy could be avoided for initial assessment in most patients with chronic hepatitis C. This strategy warrants further evaluation in other etiological types of chronic liver diseases. TE appears to be an excellent tool for early detection of cirrhosis and may have prognostic value in this setting. As TE has excellent patient acceptance it could be useful for monitoring fibrosis progression and regression in the individual case, but more data are awaited for this application. Guidelines are needed for the use of TE in clinical practice. This technology has been promoted as a noninvasive and painless alternative for a liver biopsy for monitoring liver health in patients with hepatitis.

Crossan et al. (2015) reviewed the cost-effectiveness of treating patients in the absence of liver biopsy using a variety of statistical models but generally found FibroScan was the most cost-effective tool. Patel and Wilder (2014) pointed to the high degree of accuracy by FibroScan for patients with cirrhosis but with the higher error rate by Metavir F2 or less.

In 2013, reported on a comprehensive assessment of transient elastography in the diagnosing of significant liver fibrosis in adults with chronic liver disease (Steadman et al., 2013). A meta-analysis of 57 studies reporting diagnostic performance of TE in HCV patients compared with liver biopsy. The authors rated the quality of the studies and nearly 80% were deemed high quality. The conclusion stated that TE was an accurate method for diagnosing liver fibrosis or cirrhosis and that the testing was less costly than standard liver biopsy.

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

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

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

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

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

It has been noted that the test is not recommended for people with pacemakers or for pregnant women, and inaccurate or unobtainable readings are more common in people who are obese, older, have ascites (a build-up of fluid between the abdominal wall and organs) or have features of metabolic syndrome (Kemp, W. & Roberts 2013). This is due to the fact that the FibroScan technique requires adequate visualization of the liver to obtain readings. Being obese or with the presence of ascites, the vibration wave cannot penetrate resulting in unreliable or failure of readings.

Acoustic Radiation Force Impulse elastography (AFRI) is an ultrasound test that utilizes a probe to produce an acoustic push pulse, which generates shear waves that propagate in tissue to assess liver stiffness. This test evaluates the wave propagation speed to assess liver stiffness, the faster the shear wave speed, the harder the object.

Serum fibrosis biomarkers consists of direct and indirect serum testing and risk scoring based on combining indirect and direct markers. The American Association of Liver Disease and the Infectious Disease Society of American published an update in September 2015 of the practice guidance for testing, managing, and treating adults infected with hepatitis C. The recommendation for staging patients with chronic liver disease states: "The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration controlled transient liver elastography."

Metavir Scoring: A standardized measure of fibrosis and inflammation seen on a liver biopsy. The fibrosis score ranges from 0 to 4, and the inflammation activity score is measured from 0 to 3.

Fibrosis score:

F0 = no fibrosis

F1 = portal fibrosis without septa

F2 = portal fibrosis with few septa

F3 = numerous septa without cirrhosis

F4 = cirrhosis

Activity score:

A0 = no activity

A1 = mild activity

A2 = moderate activity

A3 = severe activity

The fibrosis score is particularly useful because patients with higher fibrosis scores are more likely to progress to cirrhosis and HCC and may warrant earlier treatment.

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