I. POLICY DISCLAIMER

Johns Hopkins HealthCare LLC (JHHC) provides a full spectrum of health care products and services for Employer Health Programs, Priority Partners, Advantage MD and US Family Health Plan. Each line of business possesses its own unique contract and guidelines which, for benefit and payment purposes, should be consulted to know what benefits are available for reimbursement.

Specific contract benefits, guidelines or policies supersede the information outlined in this policy.

II. ACTION

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III. POLICY

For Priority Partners, (PPMCO), see Pharmacy Policy, MEDS092 PPMCO Hepatitis C (HCV) Therapy for specific coverage determination.

For Advantage MD, see Medicare Coverage Database:
For CPT code 0346T: Local Coverage Determination (LCD): Services That Are Not Reasonable and Necessary (L35094).
IV. POLICY CRITERIA

A. When benefits are provided under the member’s contract, JHHC considers serum biomarker panels, e.g., (FibroSure, FibroTest-ActiTest, Hepascore, and Fibrospect II) medically necessary as a noninvasive alternative to biopsy in adults with hepatitis C virus (HCV) infection or other chronic liver diseases.

B. When benefits are provided under the member’s contract, JHHC considers ultrasound transient elastography medically necessary as a noninvasive alternative to biopsy in adults with chronic hepatitis C virus (HCV) infection or other chronic liver diseases.

C. When benefits are provided under the member’s contract, JHHC considers Magnetic Resonance Elastography (MRE) medically appropriate for the diagnosis and staging of Nonalcoholic Fatty Liver Disease (NAFLD).

D. Noninvasive liver fibrosis testing related to hepatotoxic drug suspected liver injury (e.g. Methotrexate), when there are sustained abnormal liver function tests, will be reviewed on a case-by-case basis by a JHHC Medical Director.

E. Performing serum biomarker panels more than twice in a twelve month period is considered not medically necessary.

F. Performing ultrasound transient elastography (TE) more than twice in a twelve month period is considered not medically necessary.

G. Performing serum biomarker panels or ultrasound transient elastography (TE) within six months of conducting a liver biopsy is considered not medically necessary.

H. Unless specific benefits are provided under the member’s contract, JHHC considers Magnetic Resonance Elastography (MRE) and Acoustic Radiation Force Impulse Imaging (ARIF) experimental and investigational for staging fibrosis with chronic hepatitis C virus or other chronic liver diseases, except as noted in C above as these technologies do not meet Technology Evaluation Criteria (TEC).

I. Unless specific benefits are provided under the member’s contract, JHHC considers elastography and serum biomarker panels experimental and investigational for all other indications, as these tests do not meet Technology Evaluation Criteria (TEC).

V. DEFINITIONS

Hepatotoxicity: Toxic injury to the liver due to medication, chemical, herbal, or dietary supplement; another term for drug-induced liver injury (NIH, 2018).

Liver Fibrosis: The replacement of normal liver tissue with scar tissue that occurs as a result of persistent inflammation or chronic infection in liver diseases such as hepatitis C virus (HCV), hepatitis B virus (HBV), nonalcoholic steatohepatitis (NASH) or alcoholic liver disease. The scarring increases liver stiffness and reduces blood flow through the liver, which leads to hardening and death of liver cells.

Liver Fibrosis Staging: A five-point scale indicating the degree of liver fibrosis: (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis) (Fiel, 2018).

Nonalcoholic Fatty Liver (NAFL): Presence of #5% hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is considered minimal (Chalasani, 2018).
Nonalcoholic Fatty Liver Disease (NAFLD): Liver disease with evidence of hepatic steatosis, lack of secondary cause of hepatic fat accumulation that is commonly associated with metabolic comorbidities, obesity, diabetes mellitus and dyslipidemia. NAFLD can be histologically categorized as NAFL or NASH (Chalasani, 2018).

Nonalcoholic Steatohepatitis (NASH): Presence of $\geq 5\%$ hepatic steatosis and inflammation with hepatocyte injury with or without any fibrosis; Can progress to cirrhosis, liver failure, and rarely liver cancer (Chalasani, 2018).

Steatosis: Abnormal amount of fat in the liver (NIH, 2018).

Steatohepatitis: Excess fat with inflammation and damage in the liver (NIH, 2018).

VI. BACKGROUND

Hepatic fibrosis staging is an important component of treatment decisions in the care of patients with chronic hepatitis C virus (HCV) infection. Chronic inflammation caused by HCV can cause initially asymptomatic fibrosis in patients that may progress to cirrhosis and death. Staging liver fibrosis is important for prognosis, treatment regimen selection, and cancer screening. Liver fibrosis is commonly staged at biopsy according to Metavir fibrosis categories F0 for no fibrosis, F1 for portal fibrosis without septa, F2 for portal fibrosis with few septa, F3 for fibrosis with numerous septa without cirrhosis, and F4 for cirrhosis. The gold standard for assessing liver fibrosis is biopsy, however biopsies are expensive, can have medical complications, and may be subject to sampling error and inter-pathologist variability. Noninvasive alternatives to biopsy include radiologic (ultrasound transient elastography, acoustic radiation force impulse imaging (ARFI) and magnetic resonance elastography) and serum tests. Proprietary panels for hepatic fibrosis include FibroSure, Hepascore, FibroTest-ActiTest, and Fibrospect.

Several systematic reviews and meta-analyses have sought to compare tests of fibrosis by describing the Area Under the Receiver Operating Characteristic curve (AUROC), which is a summary metric of the overall discriminatory power of a test comparing specificity and sensitivity irrespective of disease prevalence in a population. Tests are generally evaluated on their ability to discriminate significant fibrosis (Metavir score $\geq F2$), advanced fibrosis (Metavir score $\geq F3$), or cirrhosis (Metavir score $\geq F4$). Other metrics of discriminatory power such as positive and negative predictive value are useful within specific populations, but are dependent on population prevalence within a specific group. No prospective randomized trials have directly compared the efficacy of various fibrosis panels for preventing patient-oriented outcomes such as decompensated liver failure or death.

Ultrasound transient elastography (Fibroscan) is a procedure that enables staging of liver fibrosis by using ultrasonographic technology. A probe that produces vibrations transmits the vibrations towards a patient’s liver. As the ultrasonic waves travel through the liver, their velocity is directly related to tissue stiffness. By measuring the velocity with which the wave travels through liver tissue, an elastography system calculates the stiffness of the liver and determines a stage of liver fibrosis. As reported by Wong et al., the stiffness of liver as determined by transient elastography is significantly correlated with the proportion of the liver affected by fibrosis with AUROC 0.87 (95% CI 0.81-0.93) for detecting advanced fibrosis and AUROC 0.89 (95% CI 0.83-0.94) for detecting cirrhosis. Although liver biopsy continues to be the gold standard for diagnosis of cirrhosis, transient elastography provides a less invasive option that may reduce the overall chance of complications for patients being evaluated for cirrhosis.

Another ultrasound based technology, Acoustic Radiation Force Impulse Imaging (ARFI) uses an ultrasound probe to produce an acoustic push-pulse, which generates shear waves that penetrate tissue to assess liver stiffness. ARFI elastography evaluates the speed of the wave; the faster the shear wave speed, the harder the object. ARFI technologies include the FDA approved Siemens Acuson S2000™ and Acuson S3000™. ARFI technology has shown similar diagnostic ability to TE, although
according to Kennedy (2018) there is insufficient data to fully validate ARFI as a recommended noninvasive measurement tool for staging of liver fibrosis.

Magnetic resonance elastography is a novel alternative radiologic test for evaluating hepatic fibrosis. A meta-analysis in 2015 showed promising data for MRE’s ability to distinguish significant fibrosis with AUROC 0.88 (95% CI 0.84-0.91) (Singh 2015), however this technology has less supportive evidence than transient elastography. MRE is based on the principle that fibrosis changes the elasticity and viscosity of tissue. By assessing the transmission of acoustic waves through liver tissue, the extent of fibrosis may be indirectly measured. The technique involves placing a probe against the patient’s back. The probe emits low-frequency vibrations that pass through the liver and can be measured by the MRI, creating a visual map (elastogram). According to the American Gastroenterological Association (AGA) Institute Guideline, MRE performed on adults with chronic hepatitis C, showed little or no difference in accuracy over transient elastography in identifying patients who truly have cirrhosis with comparable rates of misclassifying patients with cirrhosis as not having cirrhosis (false negatives) (Lim, 2017). The AGA guideline reports that MRE appears to have a somewhat higher accuracy in nonalcoholic fatty liver disease (NAFLD) and suggests using MRE for the detection of cirrhosis in this condition. No recommendation is given regarding use of MRE in staging liver fibrosis.

The American Association for the Study of Liver Diseases (AASLD) commissioned a practice guidance document from a panel of experts on the diagnosis and management of NAFLD. In a discussion of the application of TE and MRE in staging liver fibrosis in NAFLD, it was reported that MRE performed better than TE in identifying stage 2 or above liver fibrosis and both test performed equally in identifying stage 3 or above, citing the 2015 study by Imajo et al. (Chalsani, 2018). TE identified patients with fibrosis stage ≥2 with an area under the receiver operating characteristic (AUROC) curve value of 0.82 (95% confidence interval: 0.74-0.89), whereas MRE identified these patients with an AUROC curve value of 0.91 (95% CI: 0.86-0.96; P = .001) (Imajo, 2016). The concluding guidance statements from the AASLD document noted that TE or MRE are clinically useful tools for identifying advanced fibrosis in patients with NAFLD (Chalsani, 2018). According to Hayes (2018), uncertainty remains over how to interpret the results of MRE due to lack of standardized, uniform cutoff values for determining the stage of fibrosis based on the MRE measurement.

Fibrosure (LabCorp) is the American marketed version of the French Fibrotest/Actitest that incorporates age, gender, alpha2-macroglobulin, haptoglobin, gamma-glutamyl transeptidase (GGT), total bilirubin, apolipoprotein A1, alanine aminotransferase (ALT). Three different tests are available for specific indications, hepatitis c virus, alcoholic steatohepatitis (ASH), and non-alcoholic steatohepatitis (NASH) based on slightly different algorithms: HCV-FibroSure, ASH-FibroSure, and NASH-FibroSure. Interpretation of the FibroSure test may be complicated by hemolysis, Gilbert syndrome, and recent or ongoing infection (Stauber 2007). First described by French researchers in 2001, FibroSure is likely the most-studied serum panel for hepatic fibrosis in existence (Imbert-Bismut 2001). Poynard and colleagues conducted an extensive meta-analysis of diagnostic accuracy of Fibrotest compared with liver biopsy in a pooled sample of 6,378 subjects with HCV, chronic hepatitis B virus infection, NASH, and ASH and reported a mean standardized AUROC of 0.84 (95% CI 0.83-0.86) for detecting significant fibrosis with no difference according to cause of liver disease (Poynard 2007). A subsequent study by the same group compared 5-year prognostic value of serum tests and biopsy for survival without liver-related death, reporting an AUROC for Fibrotest of 0.88 (95% CI 0.79-0.98), which was not significantly different than the prognostic accuracy of liver biopsy (p=0.85) (Poynard 2012). Additional systematic reviews and metaanalyses have reported similar AUROCs for Fibrotest/Fibrosure (Chou 2013, Parkes 2012, Sebastiani 2011, Shaheen 2008, Stauber 2007).

HepaScore (formerly available through Quest Diagnostics) is a proprietary diagnostic panel of liver fibrosis incorporating bilirubin, gamma-glutamyltransferase, hyaluronic acid, alpha-2-macroglobulin, age, and sex. Interpretation of the HepaScore test may be complicated by psoriasis activity (Chladek 2013), fasting status, and natural week-to-week variability in hyaluronic
acid levels (Rossi 2013). The algorithm was proposed by Australian researchers with an initial reported AUROC of 0.85 (95% CI 0.778-0.926) for detecting significant fibrosis and an AUROC 0.938 (95% CI 0.872-1.000) for detecting cirrhosis (Adams 2005). Multiple subsequent studies have reported slightly lower AUROCs: 0.76-0.83 for detecting significant fibrosis and 0.76-0.92 for detecting cirrhosis (Halfon 2007, Cales 2008, Becker 2009, Parkes 2012, Nguyen-Khac 2008, Naveau 2009). A search of the Quest Diagnostics test directory indicates HepaScore, formerly described as only available through Quest, is no longer an option in the test directory. According to Huang (2016), Hepascore has been widely validated in chronic hepatitis C, chronic hepatitis B, alcoholic and nonalcoholic fatty liver disease, and other types of chronic liver disorders.

Liver Fibrosis, FibroTest-ActiTest Panel (now offered through Quest Diagnostics) is a combination of two tests evaluating the presence of liver fibrosis and liver necroinflammation respectively in Hepatitis C (or B). Calculated scores are based on age, gender and concentrations of bilirubin, gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), alpha-2-macroglobulin, haptoglobin, and alapoliprotein A-1. Diagnostic accuracy of established serum markers were compared with a noted increased sensitivity but decreased specificity in identifying significant fibrosis and cirrhosis of Fibrotest over HepaScore (Lurie).

FibroSpect II (Prometheus Laboratories) is a proprietary diagnostic panel using components of fibrogenic cascade such as hyaluronic acid, tissue inhibitor of metalloproteinase (TIMP-1), and alpha-2 macroglobulin. Limitations include overestimation of fibrosis among African Americans (Tama 2016). The panel was first proposed by researchers at Duke Clinical Research Institute in 2004, documenting a combined AUROC of 0.831 (95% CI 0.785-0.876) for detecting significant fibrosis (Patel 2004). Subsequent analyses have reported AUROC 0.83-0.85 (Zaman 2007, Tanwar 2016). Prometheus offers two tests to assist in detecting, staging, and monitoring liver fibrosis. FibroSpect HCV, specifically for Hepatitis C, and the proprietary algorithm specific for nonalcoholic steatohepatitis (NASH). Each test reports a FibroSpect index and the equivalent fibrosis score (Prometheus, 2018).

Despite promising AUROCs for multiple serum panels, the clinical utility of these tests is limited by prevalence in local populations and a large number of indeterminate test results. One analysis showed that despite a mean AUROC of 0.77, tests can only accurately rule-in or rule-out significant fibrosis in 35% of patients, leaving the majority of patients with indeterminate results (Parkes 2006). Consequently guidelines and recommendations issued by specialty societies including the American Association for the Study of Liver Disease (AASLD), The Infectious Diseases Society of America (IDSA), and The European Association for the Study of the Liver (EASL) recommend combinations of noninvasive tests for fibrosis, specifically combining a direct biomarker assay with vibration-controlled transient liver elastography for the most accurate noninvasive diagnosis. AASLD/IDSA states “no single method (of noninvasive testing) is recognized to have high accuracy alone and each test must be interpreted carefully.” This approach is supported by multiple studies showing combination transient elastography with serum marker panels increases diagnostic accuracy while avoiding unnecessary biopsies (Castera 2005, Boursier 2011, Carlson 2009, Smith & Sterling 2009, Bhogal and Sterling 2012).

Research has not yet identified an optimal interval for re-assessment of fibrosis in HCV positive patients who have deferred treatment; however the AASLD/IDSA guidelines state “annual evaluation is appropriate to discuss modifiable risk factors and to update testing for hepatic function and markers for disease progression.” Several retrospective studies have shown decreased liver stiffness after antiviral treatment in chronic hepatitis C, however Wu (2018) reports it is unclear if the decreased liver stiffness "reflects a regression of liver fibrosis or a decrease in hepatic necro-inflammation secondary to viral suppression". Frequency of non-invasive testing to monitor progression or regression of liver fibrosis is not established.

Use of noninvasive test for liver fibrosis is expected to expand due to procedural risks, sampling errors, and the invasive nature of the liver biopsy. It has been proposed by the American Academy of Dermatology, that "...although unproven, to aid in the diagnosis of methotrexate (MTX)-induced fibrosis...[FibroSpect II and Fibrosisure] could be considered as possible
alternatives for patients in whom liver biopsy is technically difficult or contraindicated.” (ADA, 2018). In a small Netherland study of 24 psoriasis patients who had a recent liver biopsy during MTX use the results from the Fibroscan and Fibrotest were compared with liver histology. Berends (2007) concludes that Fibrotest accurately predicted the presence of significant liver fibrosis while the Fibroscan accurately predicted the absence of significant liver fibrosis in MTX users. This suggests that a combination of Fibrotest and Fibroscan should prospectively be evaluated in monitoring and detecting significant Methotrexate-induced liver fibrosis in psoriasis patients.

A single-institution cohort study to evaluate the use of NASH FibroSURE for patients with psoriasis to aid in determining eligibility for methotrexate therapy and monitor for the development and worsening of hepatic fibrosis noted that of the 129 patients with psoriasis undergoing treatment with MTX, 69 (53.5%) underwent NASH FibroSure testing prior to starting MTX; 19 of those patients (27.5%) had elevated fibrosis scores, and 54 (78.3%) had elevated steatosis scores. Among the 107 patients who underwent NASH FibroSure testing during MTX therapy, the cumulative MTX dose corresponded to a statistically significant association of a higher NASH FibroSure hepatic fibrosis score in women (Spearman # = 0.21; P = .02) but not in men (Spearman # = 0.17; P = .11). All patients in the cohort except 1 were managed without a liver biopsy (Bauer, 2017).

A case-control study on adults with various benign inflammatory diseases (psoriasis, Crohn's disease, rheumatoid arthritis) were prospectively assessed using FibroScan and FibroTest when they were treated with MTX (cases) or before beginning treatment (controls). Among 518 included patients, 44 patients (8.5%) had FibroScan and/or FibroTest results suggesting severe liver fibrosis. In a multivariate analysis, factors associated with abnormal markers of liver fibrosis were the BMI >28 kg/m² and high alcohol consumption. Neither long MTX duration nor cumulative doses were associated with elevated FibroScan or FibroTest results. Laharie (2010) concludes that severe liver fibrosis is a rare event in patients treated with MTX and is probably unrelated to the total dose. Patients with other risk factors for liver disease should be closely monitored with non-invasive methods before and during MTX treatment. Guidelines for monitoring MTX liver toxicity should be revisited focusing on the other risk factors for liver fibrosis such as high alcohol consumption or metabolic syndrome. Non-invasive methods should be considered for screening, restricting liver biopsy to patients with increased FibroScan or FibroTest values or other usual risk factors. Further longitudinal prospective studies are mandatory to confirm this approach (Laharie).

VII. CODING DISCLAIMER

CPT Copyright 2018 American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association.

Note: The following CPT/HCPCS codes are included below for informational purposes. Inclusion or exclusion of a CPT/HCPCS code(s) below does not signify or imply member coverage or provider reimbursement. The member’s specific benefit plan determines coverage and referral requirements. All inpatient admissions require preauthorization.
### VIII. CODING INFORMATION

#### PRE-AUTHORIZATION REQUIRED

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**ICD10 AND REVENUE CODES ARE FOR INFORMATIONAL PURPOSES ONLY**
IX. REFERENCE STATEMENT

Analyses of the scientific and clinical references cited below were conducted and utilized by the Johns Hopkins HealthCare LLC (JHHC) Medical Policy Team during the development and implementation of this medical policy. Per NCQA standards, the Medical Policy Team will continue to monitor and review any newly published clinical evidence and adjust the references below accordingly if deemed necessary.

X. REFERENCES


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**XI. APPROVALS**

Historic Effective Dates: 12/02/2016, 11/20/2018