Clinical Policy Title: Serum biomarkers for liver fibrosis in chronic hepatitis

Clinical Policy Number: 01.01.01

Effective Date: June 1, 2014
Initial Review Date: December 18, 2013
Most Recent Review Date: January 18, 2017
Next Review Date: January 2018

Policy contains:
- FIBROSpect® II (PROMETHEUS Laboratories, San Diego, CA).
- Fibrotest/FibroSURE® (LABCORP®, Burlington, NC).

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas District of Columbia has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas District of Columbia’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 AmeriHealth Caritas District of Columbia 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. AmeriHealth Caritas District of Columbia’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. AmeriHealth Caritas District of Columbia’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas District of Columbia will update its clinical policies as necessary. AmeriHealth Caritas District of Columbia’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas District of Columbia considers the use of FIBROSpect® II or Fibrotest/FibroSURE® serum biomarkers for identifying patients infected with hepatitis C who are at risk for clinically significant liver fibrosis to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of FIBROSpect® II or Fibrotest/FibroSURE® serum biomarkers in persons infected with hepatitis C are not medically necessary.

Alternative covered services:

- Alanine transaminase (ALT) test.
- Aspartate aminotransferase (AST) test.
- Computed tomography (CT) scan.
- Magnetic resonance (MR).
• Fibrogen test.
• Haptoglobin test
• Liver biopsy.
• Total bilirubin test.
• Transient elastography (TE; Fibroscan®; Echosens Co., Paris, France).
• Ultrasound.

**Background**

In the United States, an estimated 150,000 persons are diagnosed annually with chronic liver disease, and nearly 30,000 have cirrhosis at initial presentation (Thein, 2008). The development and progression of hepatic fibrosis can mediate disease-related complications of cirrhosis. The progression of hepatic fibrosis is a nonlinear, discontinuous process that is greatly influenced by factors such as age, sex, race, alcohol exposure and obesity. Obtaining further information about the degree of liver injury from hepatitis C is an important factor in deciding to pursue or defer antiviral therapy (Thein, 2008).

The gold standard for diagnosis and planning therapy in acute and chronic liver disease is histopathological examination of a percutaneous liver biopsy, as it provides essential information regarding inflammation, fibrosis, and steatosis (Nguyen, 2011). However, liver biopsy is an invasive procedure that often requires multiple passes, has a small but significant risk for procedure-related complications, and is subject to inter- and intra-observer variability in biopsy interpretation. Inaccurate staging from sampling error is estimated to occur in up to 25 percent of cases. Substantial discordance in fibrosis stage involving the right and left liver lobes in the same patient may cause sampling variability. The optimal liver biopsy specimen characteristics (≥ 20mm in length with ≥ 11 portal tracts) have been identified to minimize the effects from sampling error, but the typical specimen obtained in clinical practice often fails to meet these standards. Finally, patients may be reluctant to undergo invasive testing (Nguyen, 2011).

A variety of serum markers have been developed to identify patients who are at risk for clinically significant hepatic fibrosis (defined by stages F2 to F4). These markers are classified as direct (representing components of extracellular matrix) or indirect (reflecting hepatic inflammation and function). Indirect markers may be used alone or combined with direct markers to form panels. The practical advantages of these blood tests include their noninvasiveness, potential for widespread availability, and reproducibility when serial examinations are performed using the same laboratory.

**Serum biomarkers:**

Two serum biomarkers marketed in the United States are HCV FibroSURE® (LabCorp®, Burlington, NC), which is marketed as Fibrotest in Europe, and FIBROSpect® II (PROMETHEUS Laboratories, San Diego, CA). FibroSURE® consists of a six-biomarker panel (alpha-2-macroglobulin, haptoglobin, gamma-globulin, apolipoprotein A1, gamma-glutamyl transferase, and total bilirubin) that provides Metavir fibrosis staging and necroinflammatory grading to monitor liver status in patients with hepatitis C (LabCorp,
Table 1. Metavir scale for monitoring liver status

<table>
<thead>
<tr>
<th>Fibrosis stage (Fibro Test)</th>
<th>Activity grade (ActiTest):</th>
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<tbody>
<tr>
<td>F0 – no fibrosis: 0.00-0.21</td>
<td>A0 – no activity: 0.00-0.17</td>
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<tr>
<td>F0-F1: 0.21-0.27</td>
<td>A0-A1: 0.17-0.29</td>
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<tr>
<td>F1 – portal fibrosis: 0.27-0.31</td>
<td>A1 – minimal activity: 0.29-0.36</td>
</tr>
<tr>
<td>F1-F2: 0.31-0.48</td>
<td>A1-A2: 0.36-0.52</td>
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<tr>
<td>F2 – bridging fibrosis with few septa: 0.48-0.58</td>
<td>A2 – moderate activity: 0.52-0.60</td>
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<tr>
<td>F3 – bridging fibrosis with many septa: 0.58-0.72</td>
<td>A2-A3: 0.60-0.63</td>
</tr>
<tr>
<td>F3-F4: 0.72-0.74</td>
<td>A3 – severe activity: 0.63-1.00</td>
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<tr>
<td>F4 – cirrhosis: 0.74-1.00</td>
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Source: LabCorp.

LabCorp is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 and is certified to perform high complexity testing; the U.S. Food and Drug Administration (FDA) determined that approval is not currently required (LabCorp, 2013). According to the manufacturer, hepatitis C virus (HCV) FibroSURE® is indicated for:

- Assessment of liver status following a diagnosis of HCV.
- Pretreatment baseline and/or post-treatment assessment during HCV therapy.
- Liver status of patients with human immunodeficiency virus (HIV)/HCV coinfection.
- Monitoring and treatment of patients with hepatitis B virus (HBV).

Limitations associated with the use of HCV FibroSURE® are the possibility of false-positive results attributable to decreases in haptoglobin from hemolysis, increases in total bilirubin from conditions such as Gilbert’s syndrome and cholestasis, and increases in α2-macroglobulin and haptoglobin from systemic, as well as hepatic inflammation. Therefore, HCV FibroSURE® should not be used for patients with Gilbert’s syndrome, hemolysis, acute hepatitis, autoimmune hepatitis, autoimmune hepatitis, or extrahepatic cholestasis (Nguyen, 2011; LabCorp, 2013). The reproducibility of noninvasive testing is an important issue in clinical practice. Because of the variability of components in assays and analyzers, HCV FibroSURE® can only be performed in validated reference laboratories as opposed to local outpatient or hospital-based labs where other testing is typically performed (Nguyen, 2011).

FIBROSpect® uses a quantitative analysis of hyaluronic acid, tissue inhibitor of metalloproteinase and α2-macroglobulin, which applies an algorithm to predict the likelihood of liver fibrosis in patients with hepatitis C with no indeterminate results (PROMETHEUS, 2013). PROMETHEUS Laboratories Inc. is CLIA-certified and accredited by the College of American Pathologists. This test is only offered at PROMETHEUS laboratories (PROMETHEUS, 2013).
Searches

AmeriHealth Caritas District of Columbia searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s (AHRQ’s) National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on November 10, 2016. Search terms were: "Liver Cirrhosis"[Mesh], "Liver Cirrhosis/diagnosis"[Mesh], "Hepatitis C"[Mesh], "Hepatitis C, Chronic"[Mesh] crossed with "Biological Markers,"[Mesh] “Fibrotest,” “FibroSURE®” and “FIBROSpect®.”

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

We identified six systematic reviews for this policy. No economic analyses were identified.

For the FIBROSpect® test, three systematic reviews with overlapping literature found insufficient evidence to determine either its efficacy for detecting fibrosis or disease severity in HCV-infected populations. FIBROSpect® has a significant false-negative rate, indicating that it fails to detect cases of clinically significant fibrosis detected by biopsy. Studies generally enrolled populations with a high prevalence of clinically significant fibrosis, which may overestimate accuracy estimates, and used a variety of gold standards. Thus, its “true” discriminative ability has not been tested adequately. Finally, there is a lack of evidence of the effect of FIBROSpect® testing on patient management or patient outcomes.

For the FibroTest/FibroSURE® test, five systematic reviews with overlapping literature found insufficient evidence to determine either its efficacy for detecting fibrosis or disease severity or impact on patient outcomes in HCV-infected populations. Test scores at the extremes of the fibrosis measures (e.g., FibroTest <0.20 or >0.60), which are seen in approximately 50 percent of patients, have acceptable predictive values (80 percent range), but test scores with intermediate values are not accurate enough to replace liver biopsy. Risk factors for erroneous test results include unconjugated hyperbilirubinemia.
and inflammation.

Overall, variability in methods and poor interobserver agreement for histological staging limit the diagnostic efficacy of noninvasive biomarkers such as the FIBROSpect® and Fibrotest/FibroSURE® tests. Noninvasive biomarkers produce continuous scores that are then correlated with categorical variables, i.e., the stage scores, which are only descriptive categories of fibrosis. There are differences among the various histological scoring systems, and they lack an arithmetical progression. Quantitative measurement of liver fibrosis would be a more appropriate comparator to these test scores, but the relationship between clinical correlations and quantitative measurement of liver fibrosis has not been extensively evaluated (Cholongitas, 2010).

The National Institutes of Health (NIH) issued a consensus statement on the management of hepatitis C that considered the use of noninvasive tests for assessing liver fibrosis (NIH 2002). It concluded noninvasive tests were not adequate substitutes for liver biopsy, as they were not widely available or well validated; no single test or panel of serologic markers can provide an accurate assessment of intermediate stages of hepatic fibrosis. Since then, several organizations have issued evidence-based recommendations and arrived at similar conclusions, despite wider availability of these tests (Moyer, 2013; Centers for Disease Control and Prevention, 2013; Rockey, 2009; Ghany, 2009; Mofenson, 2009).

**Policy updates:**

One systematic review update (Selph, 2014) of a previously included review (Chou, 2013), one cost-effectiveness analysis (Crossan, 2015), and one guideline (American Association for the Study of Liver Diseases [AASLD] 2014) were added to the policy. The new information does not change the previous findings or the clinical policy. Therefore, no changes to the policy are warranted.

In a previous systematic review, Chou (2013) had omitted a significant number of published studies from summary estimates, because they provided insufficient information to calculate diagnostic accuracy. Selph (2014) obtained the unpublished data and recalculated diagnostic accuracy estimates. The additional data had no appreciable impact on diagnostic accuracy estimates for diagnostic tests for hepatic fibrosis.

Crossan (2015) assessed the diagnostic accuracy and cost-effectiveness of noninvasive liver tests (NILTs), including FibroTest and FIBROSpect®, in adults with chronic liver disease from the perspective of current practice in the UK. FibroTest was the most widely assessed commercial test, and FIBROSpect® was studied only in HCV populations for the stages of interest in their models. NILTs were compared with each other, sequential testing strategies, biopsy, and strategies including no testing. The overall robustness of included studies was poor, and the economic benefits of NILTs varied according to the cause of the liver disease. For HCV the best option is to treat all patients regardless of stage of liver disease. For persons with hepatitis B e antigen (HBeAg)-negative chronic HBV, this is also the case if the higher bound of the standard cost-effectiveness threshold is considered acceptable. These findings would apply in settings similar to the UK; however, in resource-poor settings, a treat-all strategy may
not be possible. In this case, a noninvasive test may be a better diagnostic option than liver biopsy.

The AASLD and the Infectious Diseases Society of America, in collaboration with the International Antiviral Society–USA, recommend assessing the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, to determine the urgency for treatment (AASLD, 2014). Indirect serum markers, direct serum markers and vibration-controlled TE may be considered. However, they acknowledge no single method has sufficiently high accuracy, and each test must be interpreted carefully. Based on the results of Selph (2014), these tests are, at best, only moderately useful for identifying clinically significant fibrosis or cirrhosis. The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled TE. A biopsy should be considered for any patient who has discordant results between the two modalities that would affect clinical decision making.

In 2016, we added one new systematic review/meta-analysis of studies that directly compared FibroTest, aspartate aminotransferase-platelet ratio index (APRI), the FIB4 index and TE to biopsy (Houot, 2016). The analysis applied a novel Bayesian approach to compare and rank the area under the receiver operating curve (AUROC) of each test based on etiology (persons with chronic HCV, HBV, or HCV and HBV co-infection).

Combined results for all etiologies revealed that APRI had the lowest test performance for identifying advanced fibrosis, and FibroTest had the highest. For identifying cirrhosis, APRI had the lowest test performance compared to either TE or FIB4, with no significant differences between the remaining test comparisons. There were no differences in test performances for either cirrhosis or fibrosis based on specific etiology. This analysis provides new information on the relative performance of the four most common noninvasive tests for liver fibrosis. The impact of this test on patient management and outcomes, particularly for individuals with intermediate stages of fibrosis, is yet to be determined. While encouraging, these results do not changed previous conclusions. Therefore, no policy changes are warranted.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Houot (2016)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Blood tests and TE in chronic HCV and HBV infection</td>
<td>• Systematic review and meta-analysis of 71 direct comparisons of FibroTest, APRI, FIB4 index or TE to biopsy, in persons with either advanced fibrosis or cirrhosis.</td>
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<tr>
<td></td>
<td>• Overall quality: good (four studies), fair (53 studies) and poor (14 studies).</td>
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<td>• Area under the receiver operating curve (AUROCs) (median, credibility interval):</td>
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<td>• Grouping all HCV and HBV, identifying advanced fibrosis favored FibroTest vs. TE (0.06, 0.02 to 0.09), FibroTest vs. APRI (0.05, 0.03 to 0.07).</td>
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<td>• For identifying cirrhosis TE vs. APRI (0.07, 0.02 to 0.13) and FIB4 vs. APRI (0.04, 0.02 to 0.05), but no significant differences found for the remaining comparisons.</td>
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<td>• Similar rankings were observed in chronic HCV and HBV etiologies.</td>
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<tr>
<th>Crossan (2015)</th>
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<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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| NILTs in chronic liver disease | • Systematic review, meta-analysis and cost-effectiveness analysis (CEA) of 302 studies.  
• Expected costs were estimated using a UK perspective; health outcomes were measured as quality-adjusted life-years (QALYs).  
• NILTs were compared with each other, sequential testing strategies, biopsy and strategies, including no testing.  
• Overall quality of included studies: low with high risk of bias due to diagnostic threshold cut-offs not validated and inadequate liver biopsy sampling. A substantial number of tests had only one study from which diagnostic accuracy was derived.  
• Given a CE threshold of £20,000 per QALY, treating everyone with HCV without prior testing was cost-effective with an incremental cost-effectiveness ratio (ICER) of £9,204.  
• For HBV [hepatitis B e antigen (HBeAg)-negative] this strategy had an ICER of £28,137, which was cost effective only if the upper bound of the standard UK CE threshold range (£30,000) is acceptable.  
• For HBeAg-positive disease, two NILTs applied sequentially (hyaluronic acid and magnetic resonance elastography) were cost-effective at a £20,000 threshold (ICER: £19,612); however, high uncertainty, with several test strategies having similar expected outcomes and costs.  
• For patients with alcoholic liver disease (ALD), liver biopsy was the cost-effective strategy, with an ICER of £822. Further evidence for treatment effectiveness is required for ALD and non-alcoholic fatty liver disease. |
| Chou (2013) | Key points:  
• Systematic review of 40 studies of diagnostic accuracy in screened populations: Fibrotest vs. liver biopsy (20 studies); FIBROSpect® vs. liver biopsy (four studies); APRI vs. Fibrotest (16 studies).  
• Quality of evidence: Fibrotest vs. liver biopsy (high); FIBROSpect® vs. liver biopsy (low); APRI vs. Fibrotest (moderate). Studies generally enrolled a broad spectrum of patients with varying severity of fibrosis and other markers of HCV infection severity; results are likely applicable to a screening population.  
• Fibrotest: the median AUROC = 0.79 (range 0.70 to 0.89) (METAVIR F2-F4, Ishak 3-6, or equivalent); FIBROSpect®: median AUROC=0.86 (range 0.82 to 0.90) (METAVIR F2-F4, Ishak 3-6, or equivalent).  
• Comparison of APRI and Fibrotest showed similar AUROC estimates.  
• Results were robust to changes in biopsy specimen length and aminotransferase levels.  
• Insufficient evidence to determine clinical outcomes associated with various testing strategies. |
| For AHRQ HCV screened populations |  
| Hayes (2010) | Key points:  
• Systematic review of five studies.  
• Limitations of evidence: high prevalence of clinically significant fibrosis, which may overestimate accuracy estimates; lack of agreement on gold standard.  
• FIBROSpect® is a moderately effective method for the detection of clinically significant fibrosis in HCV-infected patients; sensitivity = 67% to 81%, specificity = 62% to 74%.  
• Insufficient evidence of efficacy and impact on patient outcomes.  
• Additional studies are needed to determine clinical role. |
| Cholongitas (2010) | Key points:  
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| HCV recurrence after liver transplantation | - Systematic review identified one study evaluating Fibrotest in 56 patients.  
- No quality appraisal available.  
- Discriminative ability was poor (AUROC: 0.56), with poor positive predictive value.  
- Only 32% had fibrosis scores > 2.  
- Impact on clinical practice and the optimal combination with liver biopsy and assessment of collagen content need further evaluation. |
| Smith (2009) HCV or HCV/HIV coinfection | **Key points:**  
- Systematic review of three studies of FIBROSpect® and six studies of Fibrotest.  
- No quality appraisal available.  
- Unclear percentage of HCV/HIV patients studied.  
- Fibrotest: the components of these models are not readily available and haptoglobin and bilirubin can give false positive results.  
- FIBROSpect® can differentiate mild from severe fibrosis, but less accurate for intermediate stages (F1-F3).  
- Liver biopsy is still considered the gold standard. |
| Shaheen (2008) HCV/HIV coinfection   | **Key points:**  
- Systematic review of one study (130 total patients) using Fibrotest.  
- Only scores at the extremes of these fibrosis measures (e.g., FibroTest < 0.20 or > 0.60), which are seen in ~50% of patients, have acceptable predictive values (80% range).  
- In individuals with intermediate values, not yet accurate enough to replace liver biopsy. |
| Shaheen (2007) HCV infection         | **Key points:**  
- Systematic review of four studies (546 total participants).  
- In heterogeneous analyses for significant fibrosis, the AUROCs for FibroTest = 0.81 (95% confidence interval [CI] 0.78 to 84)  
- At a threshold of approximately 0.60, the sensitivity and specificity of the FibroTest = 47% (range 35 to 59%) and 90% (range 87% to 92%), respectively.  
- Methodological quality, the length of liver biopsy specimens and inclusion of special populations did not explain the observed heterogeneity.  
- Prevalence of significant fibrosis (F2-4) and cirrhosis affected diagnostic accuracy.  
- Refinements are needed before test can replace liver biopsy. |

**References**

**Professional society guidelines/other:**


Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of


**Peer-reviewed references:**


Hepatitis C Virus (HCV) FibroSURE®. Laboratory Corporation of America® (LabCorp) website. https://www.labcorp.com/wps/portal/lut/p/c1/04_SB8K8xLLM9MSSzPy8xBz9CP0os_hACzO_QCM_lwML01ALAYNj1yBnQxnfAmJ6U6B8JG55A0MCuv088nNT95P1o8zjQ11Ngg09LY0N_N2DjQw8g_18nbw9jDxc


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

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.
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>
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<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0001M</td>
<td>Infectious disease, HCV, six biochemical assays (alt, a2-macroglobulin, apolipoprotein a-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver</td>
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<tr>
<th>ICD-10 Code</th>
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<td>B18.2</td>
<td>Chronic viral hepatitis C</td>
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<tr>
<td>B19.2</td>
<td>Unspecified viral hepatitis C</td>
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<tr>
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<th>Description</th>
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