Corporate Medical Policy

Hepatitis C AHS – G2036

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Description of Procedure or Service

Description

Hepatitis C is a liver infection caused by the Hepatitis C virus (HCV). Hepatitis C is a blood-borne virus that can be spread via sharing needles or other equipment to inject drugs as well as in inadequate infection control in healthcare settings (CDC, 2018).

Hepatitis C causes liver disease and inflammation. A chronic HCV infection can lead to hepatic damage, including cirrhosis and hepatocellular carcinoma, and is the most common cause of liver transplantation in the United States (AASLD-IDSA, 2015).

Scientific Background

The Centers for Disease Control and Prevention estimate that 2.4 million people in the United States have chronic hepatitis C (CDC, 2016a, 2020a). Prevalence of the infection is highest in individuals born between 1945 and 1965. This rate is approximately six times higher than that seen in other adult age groups, and the CDC estimated approximately 50,300 new infections occurring each year (CDC, 2016b, 2018). Hepatitis C virus (HCV) infection is the most common reason for liver transplantation in adults in the U.S. and may lead to hepatocellular carcinoma (S. Chopra, 2018; Chopra, 2019).

It is estimated that 20% of people with HCV infection will develop cirrhosis, and nearly 5% will die from liver disease resulting from the HCV infection. The number of deaths from hepatitis is increasing and is projected to continue to increase for several more decades unless treatment is scaled up considerably (Razavi et al., 2014). Although HCV infection is common, it is estimated that 50-75% of individuals who are infected are unaware of their infection as symptoms are absent or nonspecific until much later, and therefore do not receive the care and treatment that can mitigate progression to severe liver disease and possibly death (Hagan et al., 2006; Rein et al., 2012).

HCV is spread through exposure to blood of infected individuals. Such exposure includes injection drug use, blood transfusions (prior to 1992), and to a lesser extent, high-risk sexual behaviors. Additionally, being born to an HCV-infected mother, hemodialysis, intranasal drug use, tattoos, incarceration, needle sticks, and invasive procedures (prior to implementation of universal precautions) are also associated with increased risk of HCV infection. Some countries are experiencing a recent resurgence of HCV infection among young intravenous drug users and HIV-infected homosexual men (CDC, 2015a; Wandeler et al., 2015).

HCV is a small, positive-stranded RNA-enveloped virus with a highly variable genome (Simmonds, 2001). Assessment of the HCV genotype is crucial for management of the HCV infection. There are

currently six major genotypes of HCV, and major treatment decisions (regimen, dosing, duration) vary from genotype to genotype (S. Chopra, Arora, Sanjeev, 2020). Some regimens for one genotype (such as ledipasvir-sofosbuvir ["Harvoni"] for genotype 1) may not be effective for another (in this case, Harvoni may be used for genotypes 1, 4, 5, and 6 but not 2 or 3) (S. Chopra, Muir, Andrew, 2020; Lexicomp, 2019).

HCV is frequently asymptomatic, necessitating the need of strong screening procedures. As many as 50% of HCV-infected individuals are unaware of their diagnosis, and risk factors such as drug use or blood transfusions may increase risk of acquiring an HCV infection. Several expert groups, such as the CDC, have delineated screening recommendations in order to provide better care against the virus (S. Chopra, Arora, Sanjeev, 2018).

Hepatitis C can be diagnosed with either serologic antibody assays or molecular RNA tests. A serologic assay can detect an active infection and a resolved HCV infection, but cannot differentiate whether the infection is acute, chronic, or no longer present. Various serologic assays include enzyme immunoassays (EIA), chemiluminescence immunoassays (CIA), and point-of-care rapid immunoassays (Spach, 2020).

Molecular RNA tests detect Hepatitis C RNA, and the process includes nucleic acid test (NAT) or nucleic acid amplification test (NAAT). The NAT test becomes positive 1-2 weeks after initial infection and it has become the gold standard test for patients who have a positive EIA screening test. The NAT can detect whether a patient has a current active infection or a resolved infection (Spach, 2020).

Many point-of-care tests have been developed to diagnose hepatitis C efficiently. These point-of-care tests are particularly important for diagnoses in economically impoverished areas. Examples of these tests include OraQuick, TriDot and SDBioline. The OraQuick HCV test is a FDA approved point-of-care test which utilizes a fingerstick and a small whole blood sample to detect the virus. This test is reportedly more than 98% accurate and provides results in 20 minutes (OraSure, 2013). The 4th Generation HCV Tri-Dot is a rapid test which can detect all subtypes of HCV with 100% sensitivity and 98.9% specificity (JMitra&Co, 2015). This test uses human serum or plasma and can provide results in three minutes. Finally, the SDBioline is an immunochromatographic rapid test that can identify HCV antibodies in human blood, serum or plasma (Abbott, 2020). This test uses a safe fingerstick procedure to obtain a sample.

Hepatitis panel tests have also been developed. For example, the VIDAS® Hepatitis panel by BioMérieux tests for hepatitis A, B and C in less than two hours (BioMérieux, 2018). This panel includes nine automated assays and is a rapid, reliable and simple testing method. Legacy Health's Hepatitis Chronic Panel detects Hepatitis B and C within 24-48 hours through a CIA method (Legacy_Health, 2021).

A hepatitis C vaccine is currently not available although many vaccines are under development; barriers to the development of such a vaccine include virus diversity, a lack of knowledge of the immune responses when an infection occurs, and limited models for the testing of new vaccines (Ansaldi, Orsi, Sticchi, Bruzzone, & Icardi, 2014; Bailey, Barnes, & Cox, 2019). The World Health Organization hopes for a 90% reduction in new hepatitis C cases by the year 2030 (Bailey et al., 2019).

Management of HCV infection typically involves monitoring the effect of treatment. The goal of treatment is to achieve a "sustained virologic response" (SVR), which is defined as "an undetectable RNA level 12 weeks following the completion of therapy" (S. Chopra, Pockros, Paul, 2020). This measure is a proxy for elimination of HCV RNA. The assessment schedule may vary regimen to regimen, but the viral load is generally evaluated every few weeks (S. Chopra, Pockros, Paul, 2020).

Clinical Validity and Utility

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Messina et al. (2015) performed a meta-analysis on the prevalence of HCV genotypes worldwide. The authors evaluated 1217 studies encompassing approximately 90% of the global population. They calculated genotype 1 to comprise 83.4 million cases (46.2% of all HCV cases), genotype 3 to comprise 54.3 million cases (30.1%), and genotypes 2, 4, and 6 to comprise a combined 22.8% cases. Genotype 5 comprised less than 1% of HCV cases. The diversity of genotypes also varied; the highest diversity is observed in China and South-East Asia, while in some countries, such as Egypt and Mongolia, almost all HCV infections are caused by a single genotype (Messina et al., 2015).

Inoue et al. (2017) described four HCV patients whose treatment failed. These four HCV patients had received a treatment regimen of daclatasvir plus asunaprevir, which is used for genotype 1b. However, these four patients were re-tested and found to have a different genotype; 3 patients had genotype 2 and the 4th patient had genotype 1a. The authors suggested that the daclatasvir plus asunaprevir regimen was ineffective for patients without genotype 1b (Inoue et al., 2017).

Moreno et al. (2016) performed a cost analysis of expanded HCV coverage. Two scenarios were simulated, one with expanded fibrosis coverage to stage 2 fibrosis, and the other to all fibrosis cases. Over a 20-year simulation, treatment costs increased, but private payers experienced overall savings of $10 billion to $14 billion after treatment costs. A positive "spillover" benefit of $400 million to Medicare was seen in the 5-year model, and a benefit of $7 billion to Medicare was seen in the 20-year model (Moreno et al., 2016).

Linthicum et al. (2016) assessed the cost-effectiveness of expanding screening and treatment coverage over a 20-year horizon. The authors investigated three scenarios, each of which expanded coverage to a different stage of fibrosis. "Net social value" was the primary outcome evaluated, and it was calculated by the "value of benefits from improved quality-adjusted survival and reduced transmission minus screening, treatment, and medical costs." Overall, the scenario with only fibrosis stage 3 and fibrosis stage 4 covered generated $0.68 billion in social value, but the scenario with all fibrosis patients (stages 0-4) treated produced $824 billion in social value. The authors also noted that the scenario with all fibrosis stages covered created net social value by year 9 whereas the scenario with only stages 3 and 4 covered needed all 20 years to break even (Linthicum et al., 2016).

Chen et al. (2019) completed a meta-analysis to research the relationship between type 2 diabetes mellitus development and patients with a HCV infection. Studies were included from 2010 to 2019. Five types of HCV individuals were incorporated in this study including those who were "non-HCV controls, HCV-cleared patients, chronic HCV patients without cirrhosis, patients with HCV cirrhosis and patients with decompensated HCV cirrhosis" (Chen et al., 2019). HCV infection was found to be a significant risk factor for type 2 diabetes mellitus development. Further, "HCV clearance spontaneously or through clinical treatment may immediately reduce the risk of the onset and development of T2DM [type 2 diabetes mellitus] (Chen et al., 2019)."

Saeed et al. (2020) completed a systematic review and meta-analysis of health utilities for patients diagnosed with a chronic hepatitis C infection. Health utility can be defined as a measure of health-related quality or general health status. A total of 51 studies comprised of 15,053 patients were included in this study. The researchers have found that "Patients receiving interferon-based treatment had lower utilities than those on interferon-free treatment (0.647 vs 0.733). Patients who achieved sustained virologic response (0.786) had higher utilities than those with mild to moderate CHC [chronic hepatitis C]. Utilities were substantially higher for patients in experimental studies compared to observational studies (Saeed et al., 2020)." Overall, these results show that chronic hepatitis C infections are significantly harming global health status based on the measurements provided by health utility instruments.

Vetter et al. (2020) conducted a retrospective study to assess the performance of rapid diagnostic tests (RDTs) for Hepatitis C virus (HCV) infection. 13 RDTs were studied including the Standard Q

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HCV Ab by SD Biosensor, HCV Hepatitis Virus Antibody Test by Antron Laboratories, HCV-Ab Rapid Test by Beijing Wantal Biological Pharmacy Enterprise, Rapid Anti-HCV Test by InTec, First Response HCV Card Test by Premier Medical Corporation, Signal HCV Version 3.0 by Arkray Healthcare, TRI DOT HCV by J. Mitra & Co, Modified HCV-only Ab Test by Biosynex SA, SD Bioline HCV by Abbott Diagnostics, OraQuick HCV by OraSure, Prototype HCV Ab Test by BioLytical Laboratories, Prototype DPP HCV by Chembio Diagnostic Systems, and Prototype Care Start HCV by Access Bio. 1,710 samples were evaluated in which 648 samples were HCV positive and 264 samples were also HIV positive. In the samples from HIV negative patients, most RDTs showed high sensitivity of > 98% and specificity of >99%. In HIV positive patients, sensitivity was lower with only 1 RDT reaching >95%. However, specificity was higher, with only 4 RDTs showing a specificity of <97%. The authors concluded that these tests are compliant with the World Health Organization (WHO) guidance which recommends an HCV RDT to have a sensitivity of >98% and specificity >97%. However, in HIV positive patients, the specificity remained high, but none of the tests met the WHO sensitivity criteria. The authors conclude that "these findings serve as a valuable baseline to investigate RDT performance in prospectively collected whole blood samples in the intended use settings (Vetter et al., 2020)."

In a prospective study, Chevaliez et al. (2020) evaluated the use of molecular point of care (POC) testing and dried blood spot (DBS) for HCV screening in people who inject drugs (PWID). 89 HCV-seropositive PWID were further assessed with a liver assessment, blood tests, POC HCV RNA testing, and fingerstick DBS sampling. 77 patients had paired fingerstick capillary whole blood for POC HCV RNA testing and fingerstick sampling with interpretable results, while the other 12 samples had no valid result due to low sample volume. The POC HCV RNA test detected 30 HCV-seropositive PWID and DBS sampling detected 27 HCV-seropositive PWID. The rate of invalid results using the POC test was below 10%, so it may be performed by staff without extensive clinical training in decentralizing testing location. This study also showed high concordance for detection of active HCV infection from DBS compare to the POC test. The authors conclude that the use of POC diagnostic testing and DBS sampling should be recommended as a one-step screening strategy to increase diagnosis, increase treatment, and reduce the number of visits.

Applicable Federal Regulations

A search on the FDA website for “Hepatitis C” on 04/25/2021, yielded 31 results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Hepatitis C testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Hepatitis C testing is covered

Reimbursement for screening at least once in a lifetime for Hepatitis C infection is allowed for adults between the ages of 18 years and 79 years.

Reimbursement for testing for Hepatitis C infection for all adults (>18 years old) with recognized conditions or exposures is allowed in the following situations:

- Illicit intranasal or injectable drug use
- Receipt of clotting factor concentrates produced before 1987
- History of hemodialysis
- Evidence of liver disease (based on clinical presentation or persistently abnormal alanine aminotransferase (ALT) levels, or abnormal liver function studies)
- Presence of HIV infection
- Receipt of an organ transplant before July 1992
- Receipt of a blood transfusion or blood component before July 1992
- Individuals notified that they received blood from a donor who later tested positive for an HCV infection
- History of incarceration
- Receipt of a tattoo in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
- Children born to HCV-positive women
- Current sexual partners of HCV-infected persons

Reimbursement for routine periodic HCV for individuals with ongoing risk factors, while risk factors persist is allowed for:

- Individuals who currently inject drugs and share needles, syringes, or other drug preparation equipment
- Individuals who are receiving ongoing hemodialysis

Reimbursement for one time testing for HCV genotype is allowed prior to initiation of treatment to guide selection of the most appropriate antiviral regimen.

Reimbursement for patients with acute HCV infection, monitoring HCV RNA to determine spontaneous clearance of HCV infection versus persistence of infection is allowed. Testing can be performed every 4 to 8 weeks for 6 to 12 months.

Reimbursement for testing for HCV viral load, using a quantitative nucleic acid test, is allowed in the following situations:

- prior to initiation of HCV therapy, AND
- after 4 weeks of therapy AND
- at the end of treatment AND
- 12 weeks and 24 weeks after completion of treatment.

When Hepatitis C testing is not covered

Reimbursement is not allowed for Hepatitis C testing in all situations not outlined above.

Policy Guidelines

Centers for Disease Control and Prevention (CDC) (CDC, 2012, 2015b, 2020b, 2020c)

The Centers for Disease Control and Prevention (CDC) recommends HCV testing in the following individuals:

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- One time HCV testing is recommended regardless of age for those :
    - "With HIV
    - People who ever injected drugs and shared needles, syringes, or other drug preparation equipment, including those who injected once or a few times many years ago
    - Have certain medical conditions, including persons:
        - People who ever received maintenance hemodialysis
        - People with persistently abnormal ALT levels
    - Were prior recipients of transfusions or organ transplants, including:
        - People who received clotting factor concentrates produced before 1987
        - People who received a transfusion of blood or blood components before July1992
        - People who received an organ transplant before July 1992
        - People who were notified that they received blood from a donor who later tested positive for HCV infection
    - health care, emergency medical, and public safety personnel after needle sticks, sharps, or mucosal exposure to HCV-positive blood
    - children born to mothers with HCV infection
- Routine HCV testing is recommended for people with ongoing risk factors, while risk factors persist:
    - People who currently inject drugs and share needles, syringes, or other drug preparation equipment
    - People with selected medical conditions, including
        - People who ever received maintenance hemodialysis
- CDC recommends that any person who requests hepatitis C testing should receive it, regardless of disclosure of risk, because many persons may be reluctant to disclose stigmatizing risks (CDC, 2020c)."

The CDC also notes that the initial HCV test should be "with an FDA-approved test for antibody to HCV." A positive result for the HCV antibody indicates either a current infection or previous infection that has resolved. For those individuals, the CDC recommends testing by an FDA-approved HCV nucleic acid test (NAT) to differentiate between active infection and resolved infection. "Persons who test anti-HCV positive or have indeterminate antibody test results who are also positive by HCV NAT should be considered to have active HCV infection; these persons need referral for further medical evaluation and care". Finally, the CDC also recommends repeat testing for individuals with ongoing risk behaviors (CDC, 2012).

The CDC published guidance for healthcare personnel with potential exposure to HCV. CDC recommends testing the source patient and the healthcare personnel. When testing the source patient, baseline testing should be performed within 48 hours after exposure by testing for HCV RNA or HCV antibodies. All HCV RNA testing should be performed with a nucleic acid test. If the source patient was HCV RNA positive or if source patient testing was not performed, baseline testing for healthcare personnel should follow the same steps through nucleic acid testing 3-6 weeks post-exposure. A final HCV antibody test should be performed at 4-6 months post-exposure to ensure a negative HCV RNA test result (CDC, 2020b).

United States Preventive Services Task Force (USPSTF) (Moyer, 2013; Owens et al., 2020; USPSTF, 2013)

The United States Preventive Services Task Force (USPSTF) recommends HCV screening in adults aged 18 to 79 years (B recommendation) including all asymptomatic adults and pregnant persons with anti-HCV antibody testing followed by confirmatory PCR testing.

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American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) (AASLD-IDSA, 2017, 2018a, 2018b, 2020)

- AASLD-IDSA guidelines recommend one-time HCV testing in the following situations:
    - "One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older. Rating: I, B
    - One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below). Rating: I,B
    - Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy. Rating: I, B
    - Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below). Rating: IIa, C
    - Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP). Rating: IIa, C
- Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

1. Risk behaviors
    - Injection-drug use (current or ever, including those who injected once)
    - Intranasal illicit drug use
    - Men who have sex with men
2. Risk exposures
    - Persons on long-term hemodialysis (ever)
    - Persons with percutaneous/parenteral exposures in an unregulated setting
    - Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
    - Children born to HCV-infected women
    - Prior recipients of transfusions or organ transplants, including persons who:
        - Were notified that they received blood from a donor who later tested positive for HCV infection
        - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
        - Received clotting factor concentrates produced before 1987
    - Persons who were ever incarcerated
3. Other considerations
    - HIV infection
    - Sexually active persons about to start pre-exposure prophylaxis (PreP) for HIV
    - Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
    - Solid organ donors (deceased and living) (AASLD-IDSA, 2020)"

Rating: Class I, Level B

Recommendations for Initial HCV Testing and Follow-up

- "HCV-antibody testing with reflex HCV RNA polymerase chain reaction (PCR) is recommended for initial HCV testing. Rating: Class I, Level A
- Among persons with a negative HCV-antibody test who were exposed to HCV within the prior 6 months, HCV-RNA or follow-up HCV-antibody testing 6 months or longer after exposure is recommended. HCV-RNA testing can also be considered for immunocompromised persons. Rating: Class I, Level C

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- Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because a positive HCV-antibody test is expected. Rating: Class I, Level C
- Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load). Rating: Class I, Level A
- HCV genotype testing may be considered for those in whom it may alter treatment recommendations. Rating: Class I, Level A
- Persons found to have a positive HCV-antibody test and negative results for HCV RNA by PCR should be informed that they do not have evidence of current (active) HCV infection but are not protected from reinfection. Rating: Class I, Level A (AASLD-IDSA, 2019, 2020)."

For acute HCV infections, AASLD-IDSA issued the following recommendations:

- HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (Rating: Class I, Level C)
- Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is also recommended to determine spontaneous clearance of HCV infection versus persistence of infection (Rating: Class I, Level B)
- If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks before starting treatment is recommended to allow for spontaneous clearance (Rating: Class IIa, Level C) (AASLD-IDSA, 2017).

For monitoring patients who are starting hepatitis C treatment, are on treatment, or have completed therapy, AASLD-IDSA issued the following recommendations:

- "HCV genotype and subtype and quantitative HCV RNA (HCV viral load) is recommended prior to initiation of antiviral therapy." (Rating: Class I, Level C)
- "Hepatic function panels (defined as albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels) are recommended before starting antiviral therapy." (Rating: Class I, Level C)
- "Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy." (Rating: Class I, Level B)
- "Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy." (Rating: Class I, Level B)
- Hepatic function panels are also recommended for monitoring of disease progression every 6 to 12 months in patients that did not achieve an SVR (AASLD-IDSA, 2018b).

Recommendations for Post-Treatment Follow-Up for Patients in Whom Treatment Failed

- "Disease progression assessment every 6 to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended. Rating: I, C
- Surveillance for hepatocellular carcinoma with liver ultrasound examination, with or without alpha fetoprotein (AFP), every 6 months is recommended for patients with cirrhosis in accordance with the AASLD guidance on the diagnosis, staging, and management of hepatocellular carcinoma. Rating: Low, Conditional (AASLD-IDSA, 2020)."

Recommendations for Post-Treatment Follow-Up for Patients in Whom Treatment Failed

- "As part of prenatal care, all pregnant women should be tested for HCV infection, ideally at the initial visit. Rating: IIb, C (AASLD-IDSA, 2020)"

Recommendations for Monitoring HCV-Infected Women During Pregnancy

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- "HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody–positive pregnant women to assess the risk of mother-to-child transmission (MTCT) and degree of liver disease. Rating: I, B
- All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT. Rating: I, B
- In HCV-infected pregnant women with pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy (ICP) with subsequent assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bile acids.
- HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine (ie, high-risk pregnancy) obstetrician (AASLD-IDSA, 2020)."

Assessment of Liver Disease Severity

A section focused on determining the severity of liver diseases associated with an HCV infection is also included as part of the background of these AASLD-IDSA guidelines. The authors state the following:

"The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Noninvasive tests using serum biomarkers or imaging allow for accurate diagnosis of cirrhosis in most individuals (see pretreatment workup in When and in Whom to Initiate HCV Therapy). Liver biopsy is rarely required but may be considered if other causes of liver disease are suspected.

- Noninvasive methods frequently used to estimate liver disease severity include:
- Liver-directed physical exam (normal in most patients)
- Routine blood tests (eg, ALT, AST, albumin, bilirubin, international normalized ratio [INR], and CBC with platelet count)
- Serum fibrosis marker panels
- Transient elastography
- Liver imaging (eg, ultrasound or CT scan) (AASLD-IDSA, 2020)"

American Association for the Study of Liver Diseases (AASLD) (AASLD, 2014)

AASLD recommends not repeating Hepatitis C viral load testing outside of antiviral therapy, stating that "the results of virologic testing do not change clinical management or outcomes" (AASLD, 2014).

World Gastroenterology Organisation (WGO) (WGO, 2016)

The WGO has provided the following recommendations on hepatitis C screening:

- "It is recommended that HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/behaviour. Strong recommendation, moderate quality of evidence
- It is suggested that nucleic acid testing for the detection of HCV RNA be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV infection, in addition to nucleic acid testing for HCV RNA as part of the assessment for starting treatment for HCV infection. Conditional recommendation, very low quality of evidence (WGO, 2016)."

The WGO also includes a table which shows the populations with a high HCV prevalence or who have a history of HCV risk. The following groups are included:

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- "Persons who have received medical or dental interventions in health-care settings where infection control practices are substandard
- Persons who have received blood transfusions prior to the time when serological testing of blood donors for HCV was initiated or in countries where serological testing of blood donations for HCV is not routinely performed
- People who inject drugs (PWID)
- Persons who have had tattoos, body piercing or scarification procedures done where infection control practices are substandard
- Children born to mothers infected with HCV
- Persons with HIV infection
- Persons who use/have used intranasal drugs
- Prisoners and previously incarcerated persons (WGO, 2016)"

Finally the WGO mentions liver function tests several times, stating that "A number of clinical considerations are important for the management of persons with chronic HCV infection"; further, "Pre-treatment evaluation of the risk of adverse events should be based on the patient's clinical details, concomitant medications, and knowledge of treatment regimen to be administered. The potential for DDIs [drug-drug interactions] should be assessed before treatment, and a regimen that has a low risk of DDI selected. Standard laboratory tests that are assessed prior to treatment initiation include a full blood count (FBC), international normalized ratio (INR), renal function and liver function tests: ALT, AST, bilirubin, albumin and alkaline phosphatase (WGO, 2016)."

The WGO also mentions that "in persons with HCV infection being treated for TB, it is important to monitor liver function tests" and that "Baseline liver function tests for individuals with chronic liver disease are encouraged prior to initiating treatment for latent TB infection. For individuals with abnormal baseline test results, routine periodic laboratory testing should be carried out during the treatment of latent TB infection (WGO, 2016)."

World Health Organization (WHO) (WHO, 2017, 2018)

Recommendations on screening for HCV infection (WHO, 2017, 2018):

Testing approach	Recommendations
Focused testing in most affected populations	In all settings (and regardless of whether delivered through facility- or community based testing), it is recommended that serological testing for HCV antibody (anti-HCV) be offered with linkage to prevention, care and treatment services to the following: • Adults and adolescents from populations most affected by HCV infection (i.e. who are either part of a population with high HCV seroprevalence or who have a history of exposure and/or high-risk behaviors for HCV infection); • Adults, adolescents and children with a clinical suspicion of chronic viral hepatitis (i.e. symptoms, signs, laboratory markers) (strong recommendation, low quality of evidence) *Note: Periodic re-testing using HCV NAT should be considered for those with ongoing risk of acquisition or reinfection.*
General population testing	In settings with a ≥2% (intermediate) or ≥5% (high) HCV antibody seroprevalence in the general population, it is recommended that all adults have access to and be offered HCV serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or facility-based testing opportunities or programs such as HIV or TB clinics, drug treatment services and antenatal clinics (conditional recommendation, low quality of evidence)

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Which Serological Assay to Use	To test for serological evidence of past or present infection in adults, adolescents and children (>18 months of age), an HCV serological assay (antibody or antibody/antigen) using either a rapid diagnostic test (RDT) or laboratory-based immunoassay formats that meet minimum safety, quality and performance standards (with regard to both analytical and clinical sensitivity and specificity) is recommended. • In settings where there is limited access to laboratory infrastructure and testing, and/or in populations where access to rapid testing would facilitate linkage to care and treatment, RDTs are recommended. (Strong recommendation, low/moderate quality of evidence)

Canadian Association for the Study of the Liver (CASL) (Shah et al., 2018)

The CASL has published new guidelines regarding management of HCV.

"Determination of HCV RNA, genotype and subtype (i.e., 1a v. 1b) is helpful in the management of patients with chronic HCV infection, and genotyping before starting therapy is still recommended." Assessment of HCV genotype, HCV RNA, and resistance testing are recommended as part of initial workup (i.e. before initiation of therapy).

"In those with ongoing risk exposures, annual HCV RNA testing to assess for reinfection is suggested" (Shah et al., 2018).

Further, the CASL (Shah et al., 2018) includes the following routine bloodwork as a suggested work-up before beginning HCV therapy:

- Complete blood count
- Liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase)
- Liver function (bilirubin, INR, albumin
- Creatinine

American Gastroenterological Association (AGA) (Jacobson, Lim, & Fried, 2017; Kanwal et al., 2017)

The AGA released best practice statements for care of patients with chronic HCV that have achieved a sustained virologic response (SVR).

- "SVR should be confirmed by undetectable HCV RNA at 12 weeks after completion of an all-oral DAA treatment regimen."
- "Routine confirmation of SVR at 48 weeks post end of treatment is recommended. Testing for HCV RNA at 24 weeks post treatment should be considered on an individual patient basis."
- "Routine testing for HCV RNA beyond 48 weeks after end of treatment to evaluate for late virologic relapse is not supported by available evidence; periodic testing for HCV RNA is recommended for patients with ongoing risk factors for reinfection" (Jacobson et al., 2017).

The AGA has also released a "pathway" for HCV treatment (an algorithm).

Prior to treatment, the AGA recommends identifying the HCV genotype, as well as taking a hepatic function panel (defined as albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase).

For all three lengths of treatment courses (8, 12, 16 weeks), the AGA recommends assessing viral load and liver function (the same hepatic panel listed above) (Kanwal et al., 2017)

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European Association for the Study of the Liver (EASL) (EASL, 2018, 2020)

The EASL released guidelines on treatment of Hepatitis C. The EASL recommends:

- "Screening strategies for HCV infection should be defined according to the local epidemiology of HCV infection, ideally within the framework of local, regional or national action plans.
- Liver disease severity must be assessed prior to therapy.
- Rapid diagnostic tests using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical EIAs as point-of-care tests to facilitate anti-HCV antibody screening and improve access to care.
- "It is still useful to determine the HCV genotype and subtype where such determination is available and does not limit access to care, to identify patients who may benefit from treatment tailoring. However, "testing for HCV resistance prior to treatment is not recommended" (EASL, 2018, 2020).

Canadian Task Force on Preventive Health Care (CTFPHC) (CTFPHC, 2017)

The CTFPHC has given the following recommendations:

- "We recommend against screening for HCV in adults who are not at elevated risk (strong recommendation, very low-quality evidence).
- We recommend against screening for HCV in adults who are not at elevated risk (strong recommendation, very low-quality evidence) (CTFPHC, 2017)."

Society of Obstetricians and Gynecologists of Canada (SOGC) (Boucher & Gruslin, 2017)

The SOGC has published guidelines for the reproductive care of women living with a hepatitis C infection. These guidelines state that "Universal screening for HCV is not recommended, although targeted screening should be offered to all women falling into any at-risk category. Testing should take place following adequate counselling and informed consent of the patient (III B) (Boucher & Gruslin, 2017)."

Further, the SOGC also states that for care during pregnancy, "Antenatal care will need to be tailored individually to meet the specific needs of the woman's medical and obstetrical condition, including the monitoring of liver function (II-2 A) (Boucher & Gruslin, 2017)."

Indian Health Services (IHS) (IHS, 2021)

Indian Health Services published recommendations on Hepatitis C screening. IHS recommends using an anti-HCV antibody test such as a point-of-care test on a fingerstick capillary or venipuncture whole-blood sample or a laboratory-based HCV ELISA test on a serum sample. IHS recommends screening the following patients:

- "Adults 18 years and older, including people with diabetes, at lease once for HCV infection, regardless of their risk factors.
- All pregnant persons, regardless of age, during pregnancy.
- People at higher risk of HCV exposure (IHS, 2021)".

IHS also provides guidance on how to diagnose a chronic HCV infection:

- "For individuals with a positive HCV antibody screening test result, perform the laboratory-based HCV RNA PCR test to confirm the presence of HCV.
- The presence of HCV indicates active infection. These individuals should be referred for direct acting anti-vial (DAA) agents treatment.
- The absence of HCV indicates no active infection.

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- For individuals with a negative HCV antibody test result who might have been exposed to HCV within the previous 6 months, perform an HCV RNA PCR or follow-up HCV antibody test at least 6 months after exposure (I, 2021)."

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 86803, 86804, 87520, 87521, 87522, 87902, G0472

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Policy Implementation/Update Information

1/1/19 New policy developed. BCBSNC will provide coverage for hepatitis C testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)

10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Literature Review and Applicable Federal Regulations updated. Policy Guidelines updated. References updated. Coding table removed from the Billing/Coding section of the policy. Medical Director review 9/2019. (sk)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)

3/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. (sk)

7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Medical Director review 7/2020. Literature Review and Applicable Federal Regulations updated. Description section updated. Policy Guidelines updated. References updated**.** (bb)

3/9/21 Specialty Matched Consultant Advisory Panel review 2/17/2021. (sk)

8/24/21 Reviewed by Avalon 2nd Quarter 2021 CAB. Medical Director review 8/2021. Scientific Background and Applicable Federal Regulations updated. When Covered section updated. Policy Guidelines updated. References updated. (sk)

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