

Reimbursement Policy

Hepatitis C

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I. Policy 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).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

- 1) Screening for Hepatitis C virus (HCV) infection in pregnant individuals is covered in accordance with Avalon Policy AHS-G2035-Prenatal Screening (Nongenetic).
- 2) Once per lifetime testing for HCV infection **MEETS COVERAGE CRITERIA** for all individuals over 18 years of age.
- 3) For any individual with the following recognized conditions or exposures, one-time, post-exposure testing for HCV infection **MEETS COVERAGE CRITERIA**:
 - a) Illicit intranasal or injectable drug use
 - b) Receipt of clotting factor concentrates produced before 1987
 - c) History of hemodialysis
 - d) Evidence of liver disease (based on clinical presentation, persistently abnormal alanine aminotransferase (ALT) levels, or abnormal liver function studies)
 - e) Presence of HIV infection
 - f) Receipt of an organ transplant before July 1992
 - g) Receipt of a blood transfusion or blood component before July 1992.
 - h) Individuals notified that they received blood from a donor who later tested positive for an HCV infection

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- i) History of incarceration
 - j) Receipt of a tattoo in an unregulated setting
 - k) Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
 - l) Children born from an HCV-positive individual
 - m) Current sexual partners of HCV-infected persons
- 4) Routine periodic HCV testing **MEETS COVERAGE CRITERIA** for individuals with ongoing risk factors, while risk factors persist:
 - a) Individuals who currently inject drugs and share needles, syringes, or other drug preparation equipment
 - b) Individuals who are receiving ongoing hemodialysis
 - c) Individuals engaging in high-risk sexual behavior
 - 5) One time testing for HCV genotype **MEETS COVERAGE CRITERIA** prior to initiation of treatment to guide selection of the most appropriate antiviral regimen.
 - 6) For patients with acute HCV infection, monitoring HCV RNA **MEETS COVERAGE CRITERIA** to determine spontaneous clearance of HCV infection versus persistence of infection. Testing can be performed every 4 to 8 weeks for 6 to 12 months.
 - 7) Testing for HCV viral load, using a quantitative nucleic acid test, **MEETS COVERAGE CRITERIA** in the following situations:
 - a) prior to initiation of HCV therapy, AND
 - b) after 4 weeks of therapy AND
 - c) at the end of treatment AND
 - d) 12 weeks and 24 weeks after completion of treatment.

III. Table of Terminology

Term	Definition
AASLD	American Association for the Study of Liver Diseases
AFP	Alpha fetoprotein
AGA	American Gastroenterological Association
ALT	Aminotransferase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase

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CASL	Canadian Association for the Study of the Liver
CBC	Complete Blood Count
CC	Coverage criteria
CDC	Centers for Disease Control and Prevention
CHC	Chronic hepatitis C
CIA	Chemiluminescence immunoassays
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CTFPHC	Canadian Task Force on Preventive Health Care
DAA	Direct acting anti-viral
DBS	Dried blood spot
EASL	European Association for the Study of the Liver
EIA	Enzyme immunoassays
ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
FDA	Food and Drug Administration
HCR	Hepatitis C Screening
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICP	Intrahepatic cholestasis of pregnancy
IDSA	Infectious Disease Society of America
IHS	Indian Health Services
INR	International normalized ratio
LDH	Lactic acid dehydrogenase
LDTs	Laboratory-developed tests
MTCT	Mother-to-child transmission
NAAT	Nucleic acid amplification test
NAT	Nucleic acid test
NCD	National coverage determinations
PCR	Polymerase chain reaction
POC	Point of care
Prep	Pre-exposure prophylaxis
PWID	People who inject drugs
Rdts	Rapid diagnostic tests
RNA	Ribonucleic acid
SOGC	Society of Obstetricians and Gynecologists of Canada

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SVR	Sustained virologic response
T2DM	Type 2 diabetes mellitus
TB	Tuberculosis
USPSTF	United States Preventive Services Task Force
WGO	World Gastroenterology Organisation
WHO	World Health Organization

IV. 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 (Chopra, 2021).

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, 2015; 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 (Chopra & Arora, 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) (Chopra & Muir, 2022; Lexicomp, 2022).

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 (Chopra & Arora, 2022).

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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).

Proprietary Testing

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 et al., 2014; Bailey et al., 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” (Chopra & Pockros, 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 (Chopra & Pockros, 2020).

Clinical Validity and Utility

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).

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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 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

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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.

In an Australian observational study, Catlett et al. (2021) evaluated the Aptima HCV Quant Dx Assay to see how well it could detect HCV RNA from fingerstick capillary dried blood spot (DBS) and venipuncture-collected samples. DBS collection would benefit marginalized populations in areas that may not have access to phlebotomy services or who may have difficult venous access. DBS has also been shown to "enhance HCV testing and linkage to care," be easy for transport and storage, and can be used for other purposes like HCV sequencing and testing for HIV or hepatitis B simultaneously, which is useful in more resource-limited settings. From 164 participants, they found HCV RNA in 45 patients. The Aptima assay rendered a sensitivity and specificity of 100% from plasma, and a sensitivity of 95.6% and specificity of 94.1% from DBS. This demonstrated the comparable diagnostic performance of this assay when it comes to detecting active HCV infection from DBS samples and plasma samples, and hopefully the eventual use of other similar assays with similar performances.

V. Guidelines and Recommendations

Centers for Disease Control and Prevention (CDC)

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

- One time HCV testing is recommended regardless of age for those:
 - "With HIV

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- 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 July 1992
 - 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)

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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.

American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA)

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 activities, 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 activities, 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, 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
 1. Risk Activities
 - Injection-drug use (current or ever, including those who injected once)
 - Intranasal illicit drug use
 - Use of glass crack pipes
 - Male engagement in sex with men
 - Engagement in chem sex (defined as the intentional combining of sex with the use of particular nonprescription drugs in order to facilitate or enhance the sexual encounter)
 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 needlestick, sharps, or mucosal exposures to HCV-infected blood
 - Children born to HCV-infected [individuals]
 - Recipients of a prior transfusion or organ transplant, including persons who:
 - Were notified that they received blood from a donor who later tested positive for HCV
 - 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 and circumstances

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- HIV infection
- Sexually active persons about to start pre-exposure prophylaxis (PreP) for HIV
- Chronic liver disease and/or chronic hepatitis, including unexplained elevated alanine aminotransferase (ALT) levels
- Solid organ donors (living and deceased) and solid organ transplant recipients (AASLD-IDSA, 2021a)”

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
- 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, 2021a).”

For diagnosing acute HCV infection, AASLD-IDSA issued the following recommendation:

- “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) (AASLD-IDSA, 2021b)

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

- “The following laboratory tests are recommended within 6 months prior to starting DAA (direct-acting antiviral) therapy:
 - Complete blood count (CBC)
 - International normalized ratio (INR)
 - Hepatic function panel (ie, serum albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels)
 - Estimated glomerular filtration rate (eGFR)
- The following laboratory tests are recommended any time prior to starting DAA therapy:
 - Quantitative HCV RNA (HCV viral load)
 - If a nonpangenotypic DAA will be prescribed, then test for HCV genotype and subtype” (Rating: Class I, Level C)

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- “Quantitative HCV viral load testing is recommended 12 or more weeks after completion of therapy to document sustained virologic response (SVR), which is consistent with cure of chronic infection” (Rating: Class I, Level B)

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 if patients are not retreated or fail a second or third DAA treatment course. (Rating: Class I, Level 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, 2021a).

Recommendations for Monitoring HCV-Infected [Individuals] During Pregnancy

- “As part of prenatal care, all pregnant [individuals] should be tested for HCV infection, ideally at the initial visit. (Rating: IIB, C)
- HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody-positive pregnant [individuals] to assess the risk of mother-to-child transmission (MTCT) and severity of liver disease. (Rating: I, B)
- All pregnant [individuals] 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 [individuals] 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. (Rating: I, B)
- HCV-infected [individuals] 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 (Rating: I, B) (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, elastography, or liver 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

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- Transient elastography
- Liver imaging (eg, ultrasound or CT scan) (AASLD-IDSA, 2021a)”

American Association for the Study of Liver Diseases (AASLD)

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)

The WGO included the following groups as “HCV infection risk groups” in their guideline on the diagnosis, management, and prevention of hepatitis C:

- “Those who have received a transfusion of blood or blood products before they started screening regularly in a given country
- Those who have undergone surgical procedures/operations before they started screening regularly in a given country
- Anyone who has had injections with used or glass syringes
- Those who have undergone dental treatment
- Those with a history of nose/ear piercing or tattoos
- Health-care workers
- People who inject drugs
- Thalassemic or hemophilic patients with multiple transfusions
- Dialysis patients
- Children born to HCV-infected mothers
- Those with abnormal and unexplained aminotransferase levels
- Prisoners
- Organ transplant patients
- Those with HIV infection
- Those with commercial/barber shaving
- Sex workers”

With regards to these at-risk groups, the WGO recommends screening for “at-risk and specific age groups – risk factors vary from country to country, as does the HCV infection risk in various groups. If screening according to the list... is not practicable (for example, are patients aware that they have been injected with used syringes?), patients should be screened on the basis of elevated aminotransferase levels at their initial presentation. The Centers for Disease Control in the USA recommend testing all baby boomers; in Europe, this is not recommended” (WGO, 2017).

For assessing spontaneous clearance of hepatitis C in the setting of treatment with direct-acting antivirals, the WGO also recommends “regular laboratory monitoring with HCV RNA is recommended at least for 6 months in order to assess spontaneous clearance” (WGO, 2017).

World Health Organization (WHO)

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

Testing approach	Recommendations
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<p>Focused testing in most affected populations</p>	<p>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:</p> <ul style="list-style-type: none"> • 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) <p><i>Note: Periodic re-testing using HCV NAT should be considered for those with ongoing risk of acquisition or reinfection.</i></p>
<p>General population testing</p> <p>Which serological assay to use</p>	<p>In settings with a $\geq 2\%$ (intermediate) or $\geq 5\%$ (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.</p> <p>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)</p> <p>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.</p> <ul style="list-style-type: none"> • 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)

In a guideline pertaining to the screening, care, and treatment of people with chronic hepatitis C infection, the WHO 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/behavior. Strong recommendation, moderate quality of evidence
- It is suggested that nucleic acid testing (NAT) for the detection of HCV ribonucleic acid (RNA) be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV infection, in addition to NAT for HCV RNA as part of the assessment for starting treatment for HCV infection. - Conditional recommendation, very low quality of evidence (WHO, 2016).”

The WHO 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 (WHO, 2016)”

Finally, the WHO 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 (WHO, 2016).”

The WHO 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 (WHO, 2016).”

Canadian Association for the Study of the Liver (CASL)

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)

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- Creatinine

American Gastroenterological Association (AGA)

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).

European Association for the Study of the Liver (EASL)

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)

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)

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The SOGC has published guidelines for the reproductive care of individuals capable of becoming pregnant who are 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 [individuals capable of becoming pregnant] 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 [individual]’s medical and obstetrical condition, including the monitoring of liver function (II-2 A) (Boucher & Gruslin, 2017).”

Indian Health Services (IHS)

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 least once for HCV infection, regardless of their risk factors.
- All pregnant persons, regardless of age, during each 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-viral (DAA) agents treatment.
- The absence of HCV indicates no active infection.
- 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 (IHS, 2021)."

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g. Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are

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not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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