QUANTITATIVE HEPATITIS C VIRUS (HCV) RNA

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INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

BeaconLBS recommends the use of quantitative Hepatitis C virus (HCV) RNA testing for:

- Diagnosis when a patient has a positive anti-HCV test.
- Suspected cases of HCV infection when anti-HCV test is negative but the patient is immunocompromised.
- Patients for whom antiviral treatment is a consideration.
- Patients treated with the new direct acting antiviral drugs, measurement of on-treatment HCV RNA levels is indicated to direct clinical decisions for therapy duration and/or discontinuation of treatment. Specifically, HCV RNA quantification should be measured at baseline; during treatment at weeks 4; at the end of treatment; and 12 weeks after the end of treatment.

These recommendations are consistent with current evidence-based guidelines from the European Association for the Study of the Liver (EASL)\(^1\)\(^-\)\(^2\), US Preventive Task Force (USPSTF), and the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA).
BACKGROUND

Hepatitis C virus (HCV) is responsible for an estimated 130-170 million infections worldwide. Although approximately 3.2 million people are thought to be chronically infected in the United States, the actual prevalence is unknown because infection can be asymptomatic and screening has been targeted to populations considered to be at high risk. Newer guidelines recommend testing of individuals born between 1945 and 1965. Nonetheless, HCV is the most common blood-borne illness.

In 2007, there were an estimated 17,000 new cases of HCV, down from 240,000 cases annually in the United States during the 1980s. Even though the incidence of infection also decreased in the 1990s, the number of patients needing medical care for complications from chronic infection continues to rise. Because cirrhosis can take 30 years to develop from chronic hepatitis C infection, complications from disease may not present or be diagnosed until decades after acute infection. It is currently estimated that over 1 billion health care dollars are spent annually in the United States on HCV.

The HCV genome is a positive-sense, single-stranded RNA molecule. A cDNA clone was isolated in 1989 from the virus at that time known as non-A, non-B hepatitis, and the complete HCV genome was cloned in 1991. It was one of the first pathogens identified by molecular techniques. There are at least six viral genotypes and they predict response to treatment. Due to a high replication rate, over 75% of acute HCV infections persist as chronic HCV compared to less than 1% of acute hepatitis B virus infections. In contrast to HIV, which integrates itself into the host genome, HCV replicates in the cytoplasm of hepatocytes (and possibly lymphocytes and monocytes) and is therefore potentially curable.

Variables determining treatment outcomes include HCV genotype and baseline viral load in addition to host factors such as degree of hepatic fibrosis and IL28 genotype. Viral kinetics, as measured by the change in viral titer following initiation of therapy at certain treatment milestones, provides clinicians with important information regarding the probability of cure and optimal treatment length. Highly sensitive quantitative HCV RNA testing is the gold standard laboratory test for the diagnosis and management of HCV patients. For both standard interferon plus ribavirin therapy and combination therapy with new direct acting antivirals, measurement of HCV RNA by a sensitive quantitative assay is an integral component of patient management.

CLINICAL EVIDENCE

Laboratory Assays

A European multicenter study found commercial assays to be superior to “in-house” methods for the quantitative measurement of HCV RNA. Commercially available quantitative tests for HCV RNA are based on reverse transcription PCR and real-time PCR. End-point detection PCR assays are the older generation of quantitative assays, and rarely used today. Newer real-time assays have replaced the old end-point assays with complete automation (reducing the risk of contamination) and a broader dynamic range precluding the need for dilution of most high viral load samples. They are based on a more recent WHO standard. Newer real-time PCR assays have excellent sensitivity at the low end of detection, allowing their use for diagnosis and management of HCV.

It is recommended that any given patient’s HCV levels should be monitored with the same assay and laboratory over time. Nonetheless, a study comparing the two commercially available real-time assays found that while
absolute HCV RNA values varied, the two assays, Roche Cobas TaqMan (Roche Molecular Systems, Inc., Branchburg, NJ) and the Abbott RealTime HCV (Abbott Molecular, Des Plaines, Illinois), showed very good correlation at time points where virologic response data are critical for therapeutic decisions.13

Current Practice

In current practice, quantitative HCV RNA testing is useful for confirming diagnosis, distinguishing between acute and chronic infection, assessing viral kinetics for the purposes of tailoring treatment duration, identifying treatment failure and/or relapse, and confirming a sustained virologic response post therapy.

Quantitative HCV RNA and anti-HCV testing are used to diagnose HCV. Plasma HCV RNA levels can first be detected anywhere from the first week to the third week of infection before immunoassays can detect antibodies to HCV.9

In the past, qualitative testing was favored for diagnosis because of superior sensitivity at the lower range of detection compared with quantitative assays, but the newer generation of real-time quantitative assays have excellent sensitivity at the lower range of detection. They are preferred over qualitative tests because they provide additional information for patient management and the American Association for the Study of Liver Diseases (AASLD) states in their 2009 update that qualitative tests for HCV RNA are no longer needed in clinical practice.14

The quantitative HCV RNA value, when considered alongside serologic test results (anti-HCV), can be used with clinical information to discern between acute and chronic infection status. If, for example, a patient has a recent exposure to HCV, detectable HCV RNA and negative anti-HCV would be consistent with acute infection. When both HCV RNA and HCV antibody are present, the infection is likely a chronic infection. Occasionally, a negative anti-HCV accompanied by a detectable HCV RNA could be indicative of chronic infection in a severely immunosuppressed patient. For resolved infections, HCV antibody remains positive but HCV RNA is undetectable. Depending on the clinical scenario and suspicion, retesting is sometimes recommended. The following table includes scenarios where retesting is indicated, as based on the 2009 guidelines from the American Association for the Study of Liver Diseases.14

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<th>Anti-HCV</th>
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| +        | -       | □ Acute HCV infection with transient undetectable HCV RNA  
□ False positive or false negative result  
□ Resolution of infection | Anti-HCV & quant. HCV RNA in 4-6 mos. |
| -        | +       | □ Early stage of acute HCV infection  
□ Chronic HCV infection in an immunosuppressed individual | Anti-HCV & quant. HCV RNA in 4-6 mos. |
| -        | -       | □ Infection excluded | Anti-HCV in 4-6 mos. |

Once a diagnosis is made, a baseline quantitative test is recommended before therapy commences.12,13 Quantitative HCV RNA testing during treatment has played a significant role in studies conducted to individualize treatment duration for patients as on-treatment HCV RNA levels can be used to increase or decrease the length of
therapy. Interferon-based therapies are known to cause flu-like symptoms in addition to more serious gastrointestinal, hematologic, and CNS side effects, and in one study over 10% of patients discontinued therapy due to adverse reactions. Therefore, guidelines for preventing futile prolongation of therapy were developed. Viral kinetics, the measurement of change in viral titer, have been used in assessing response to therapy and have led to the creation of guidelines for therapy discontinuation and/or for modifying therapy length. Studies use HCV RNA quantitation to measure patient response to therapy at certain time points. Rapid virologic responders (RVR) have undetectable HCV RNA at 4 weeks after starting therapy. Early virologic response (EVR) is determined by a 2-log10 or more reduction in HCV RNA during the first 12 weeks of therapy or HCV RNA negative by treatment week 12. Extended rapid virologic responders (eRVR) have undetectable HCV RNA at week 4 and Sustained virologic responders (SVR) are defined as having no detectable HCV RNA 24 weeks after treatment has been discontinued. Various studies have analyzed viral kinetics data to advocate shortening the course of therapy in patients with a rapid response to therapy. A meta-analysis of seven randomized trials of patients infected with genotype 1 virus determined that in the setting of rapid virologic response, a reduction of the length of interferon-based therapy should only be considered when baseline viral load is low.

Quantitative HCV RNA testing is being used to establish cost-effective, outcomes-based guidelines for clinicians treating HCV patients. Based on results of HCV RNA tests, clinicians may decide to discontinue treatment for hepatitis C due to a diminished chance of sustained virologic response based on viral kinetics studies. Guidelines for discontinuing therapy have been established for patients on standard of care, interferon-based therapy and for patients on new direct acting antivirals.

Future clinical directions may include combining viral genotype, viral kinetics data, and possibly drug resistance testing to provide patients with the shortest course of effective therapy that will diminish the chance of relapse.

GUIDELINES AND RECOMMENDATIONS

There are several current clinical guidelines from societies regarding HCV RNA testing.

American Association of Liver Disease

The following recommendations are from the American Association of Liver Diseases, published in 2009 and updated in 2018:

- A sensitive quantitative HCV RNA test should be performed for diagnosis when a patient has a positive anti-HCV test.
- Quantitative HCV RNA testing should be performed in suspected cases of HCV infection when anti-HCV test is negative but the patient is immunocompromised.
- Quantitative HCV RNA testing should be performed prior to initiation of antiviral treatment.
- Quantitative HCV RNA testing can be considered at the end of treatment and 24 weeks or longer following completion of treatment to confirm sustained virologic response for patients who have undetectable HCV RNA at the end of an antiviral regimen. Antiviral drug therapy should not be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.
- HCV RNA testing can be considered in the first year of life for babies born to HCV-positive mothers If anti HCV is positive after 18 months of age, children should have HCV RNA assay done at age 3 to confirm chronic hepatitis C infection. The siblings in this case should also be tested for HCV infection (vertical transmission).
The following additional information derives from the American Association for the Study of Liver Diseases 2018 updated guidelines\textsuperscript{19} for the recommended monitoring during antiviral therapy:

- Testing for HCV genotype helps guide selection of the most appropriate antiviral regimen.
- Discontinuation of HCV treatment is recommended if HCV RNA is detectable at week 4 of treatment, and repeat testing after 2 weeks (week 6) and HCV RNA viral load is > 10 fold.
- AASLD has no recommendation regarding therapy if HCV RNA is positive at week 4 but presents with a lower viral load at week 6.
- An HCV RNA test rather than HCV antibody is recommended to assess for HCV recurrence or reinfection.
- In acute HCV infection monitoring HCV RNA (eg, every 4 to 8 weeks) for 6 to 12 months is also recommended to determine spontaneous clearance versus persistence of HCV infection. If treatment is initiated, monitoring HCV RNA level at least 12 to 16 weeks prior to treatment to allow time for possible spontaneous clearance.
- HCV antibody positive pregnant women should have HCV RNA and routine liver function tests done at initiation of prenatal care. The HCV RNA should also be reevaluated after delivery to assess spontaneous clearance.
- At least annual HCV RNA testing is recommended, for people who inject drugs and for men who actively have sex with men, after spontaneous clearance or successful treatment of the HCV infection.

\textit{European Association for the Study of the Liver (EASL)}

The following recommendations derive from the most recent European Association for the Study of the Liver (EASL) clinical practice guidelines,\textsuperscript{15} published in 2011:

- Detection of HCV RNA, ideally by a real-time PCR assay, and anti-HCV testing by immunoassay are the basis of the diagnosis of HCV.
- Anti-HCV and HCV RNA are necessary to establish chronic hepatitis C infection.
- If a patient tests positive for anti-HCV and HCV RNA is undetectable, the test should be repeated a few weeks later.
- HCV RNA quantification should be measured at baseline; during treatment at weeks 4, 12, and 24; at the end of treatment; and 24 weeks after the end of treatment.
- Standardized commercial assays are preferred, and levels should be expressed in IU/mL. The same assay should be used each time for a patient.
- Persons with needlestick exposure to hepatitis C should be tested for HCV RNA within 4 weeks.
- Babies born to mothers with HCV should be tested for HCV RNA at 1 month of age.

The following recommendations derived from the most recent European Association for the Study of the Liver (EASL) clinical practice guidelines for the management of hepatitis C virus infection,\textsuperscript{20, 21} published in 2014:

- Detection of Anti-HCV antibodies are the first line diagnostic test for HCV infection
- HCV RNA testing should be part of the initial evaluation in suspected acute hepatitis C, in
immunocompromised patients, in patients on haemodialysis and should be determined by a sensitive molecular method

- Anti HCV positive, HCV RNA negative individuals should be retested for HCV RNA 12 and 24 weeks later to confirm recovery from infection.
- HCV RNA detection and measurement should be made by a sensitive assay, lower limit detection of <15 IU/ml).
- HCV genotype must be determined prior to treatment initiation, subtyping of genotype 1a/1b may be relevant to PI-based triple therapy.
- IL28B (recently renamed IFNL3, IFN lambda-3) genotyping is not a prerequisite for treating hepatitis C.
- The endpoint of therapy is undetectable HCV RNA at 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment
- People who inject drugs (PWIDs) who are HCV RNA-negative should be tested for HCV RNA annually and following any high-risk injecting episode and when SVR achieved. HCV reinfection should be monitored through bi-annual or at least annual HCV RNA assessment for population with ongoing risk behavior (PWIDs and men who have sex with men).

**US Preventive Task Force (USPSTF)**

The following recommendations derived from the most recent publication by the US Preventive Task Force (USPSTF) on screening for and treatment of hepatitis C virus infection in asymptomatic adults:

- Screening for HCV in high risk patients, including but not limited to past or current injection drug users, receiving blood transfusion before 1992, long term hemodialysis, born to an HCV infected mother, incarceration and intranasal drug use.
- One time screening for HCV infection to adults born between 1945 and 1965.
- Detection of Anti-HCV antibodies, followed by a confirmatory real-time PCR assay testing accurately identifies patients with chronic HCV infection.
- Screening intervals for continued high risk patients should be periodic; however, evidence on frequency of screening in these persons is lacking.
- Quantitative HCV RNA testing should be performed 24 weeks after treatment cessation to confirm sustained virologic response for patients who have undetectable HCV RNA at the end of an antiviral regimen.
- The USPSTF is in the process of evaluating a change to its recommendations to include screening for asymptomatic pregnant and non-pregnant adolescents and adults.

**US FOOD AND DRUG ADMINISTRATION (US FDA)**

There are several FDA approved nucleic acid based assays for the detection and monitoring of HCV. If a test is used that has not been cleared or approved by the FDA, the performing institution must determine the performance characteristics.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**
For Medicare populations, CMS does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act)
There are several CMS policies that apply to HCV Testing (Prognosis, including Monitoring). In some cases, CMS reimbursement is limited to FDA approved and laboratory developed tests (LDT) only. Physicians should consult their state’s regulations.

### APPLICABLE CODING

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<td>87522</td>
<td>HCV RNA Quantification by Real-time PCR</td>
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REFERENCES


POLICY HISTORY/REVISION HISTORY

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| 11/08/2018 | Annual Policy Review Completed – changes made: AASLD updates for 2018: Reference added. Made the following changes under Guidelines and Recommendations AASLD:  
  - Added statement not to stop ART if RNA level can't be tested (bullet #4).  
  - Added statement for early testing of infants (bullet #5)  
  - Combined AASLD and IDSA recommendations into one section  
  - EASL guidelines: Added HCV RNA testing for hemodialysis patients. Added updates for specific population (people who inject drugs)  
  USPSTF section: added draft recommendation to include screening for other population. |
| 11/02/2017 | Annual Policy Review Completed – No changes made                                                                                                                                                                   |
Within the body of the policy, in the "BeaconLBS Recommendations" section, clarifying language was added. The recommendation itself has not changed and there is no impact on the Q&A's associated with this policy.  
Within the body of the policy, in the "Guidelines and Recommendations" - "American Association for the Study of Liver Diseases and Infectious Diseases Society of America" section, the following was added:  "Recent 2014 guidelines from American Association for the Study of Liver Diseases and Infectious Diseases Society of America state that:18  
  - The following laboratory test is recommended within 12 weeks of starting antiviral therapy:  
    - HCV genotype and quantitative HCV viral load  
  - Quantitative HCV viral load testing is recommended after 4 weeks of therapy, at the end of treatment, and at 12 weeks following completion of therapy.  
  - Quantitative HCV viral load monitoring at 4 weeks is recommended, but discontinuation of treatment because this test result is missing is NOT recommended." |