2022

Hepatitis C Testing Toolkit for Primary Care Providers: Resources to Support Hepatitis C Testing in Georgia

GEORGIA DEPARTMENT OF PUBLIC HEALTH

Hepatitis C Testing Toolkit for Primary Care Providers

This toolkit was developed for primary care providers and contains all of the resources needed to promote hepatitis C testing. By promoting HCV testing in persons at increased risk and one-time screening of all adults aged 18 years and older, we can detect hepatitis C infection earlier, link patients to care and treatment before developing complications from liver damage and reduce the likelihood of transmission of HCV to others. HCV is curable with the use of short-term oral medications.

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Overview of Hepatitis C Testing Recommendations

Background

Hepatitis C is a major health problem in the United States, with an estimated 1.3 reported cases per 100,000 and approximately 57,500 new cases of HCV infection occurring in 2019.[2] Although the number of new infections has declined over the past two decades, hepatitis C related morbidity and mortality have been steadily rising. The expanded HCV testing recommendations intend to address the following key facts:

Hepatitis C is a significant public health problem.
The Centers for Disease Control and Prevention now recommends one-time hepatitis C testing of all adults (18 years and older) and all pregnant women during every pregnancy. CDC continues to recommend people with risk factors, including people who inject drugs, be tested regularly.[1]

- Only 61% of adults with hepatitis C knew that they were infected and over 50% of acute cases progressed to chronic infection.[3]
- Left untreated, chronic hepatitis C can cause significant liver complications, including cirrhosis, cancer, and liver failure. It is the leading cause hepatocellular carcinoma (liver cancer) and is the fastest-rising cause of all cancer-related deaths in the United States.
- HCV infection is typically asymptomatic until substantial liver disease occurs, generally several decades after the onset of infection.
- 2019 data show that chronic hepatitis C infection affects every generation, underscoring new CDC recommendations that every adult should be tested at least once in their lifetime.[4]
- Risk-based screening misses up to 2/3 of HCV-infected patients.
- There have been significant advances in HCV testing technology and medical treatment that can benefit persons infected with HCV. HCV is curable with the use or short-term oral medications.
- There is a need to simplify the process of HCV testing to facilitate its incorporation into routine health care.

[1] https://www.cdc.gov/hepatitis/hcv/management.htm#section1
[2] https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepC.htm
[3] https://www.cdc.gov/mmwr/volumes/69/wr/mm6914a2.htm
[4] https://www.cdc.gov/nchhstp/newsroom/2020/hepatitis-c-impacting-multiple-generations-press-release.html

Hepatitis C: Who to Test

Most people infected with hepatitis C do not know they are infected. Chronic hepatitis C can lead to serious complications such as cirrhosis, liver cancer, and liver failure. The complications can be prevented through early detection, treatment, cure, and lifestyle/behavioral changes. Serologic testing is the primary means for identifying persons with chronic hepatitis C infection.

Primary care providers play an important role in the national response to the hepatitis C epidemic. Approximately 45% of persons infected with HCV do not report having specific risk factors. [5] The following outlines hepatitis C testing recommendations put forth by the Centers for Disease Control and Prevention (CDC).

Populations recommended for hepatitis C testing[6]

- All adults aged 18 years and older
- All pregnant women during *each* pregnancy
- People with persistently abnormal ALT levels
- Persons who have ever injected illegal drugs (past or present), including those who injected only once many years ago
- Recipients of clotting factor concentrates made before 1987
- Recipients of blood transfusions or solid organ transplants before July 1992
- Patients who have ever received long-term hemodialysis treatment
- Persons with known exposures to HCV, such as
    - health care workers after needlesticks involving HCV-positive blood
    - recipients of blood or organs from a donor who later tested HCV-positive
- All persons with HIV infection
- Children born to HCV-positive mothers
- Any person who requests HCV testing

[5] Centers for Disease Control and Prevention, Division of Viral Hepatitis
https://www.cdc.gov/mmwr/volumes/69/rr/rr6902a1.htm
[6] Centers for Disease Control and Prevention, Division of Viral Hepatitis
http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#c1

The final USPSTF recommendations statement; evidence reports on screening, mother-to-infant transmission, and treatment; and the comparative effectiveness reports on screening and treatment can be viewed at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening

U.S. Preventive Services Task Force (USPSTF) Recommends HCV Screening (Grade B)[7]
• The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.

[7]USPTF Hepatitis C Screening Recommendations
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening

U.S. Preventive Services TASK FORCE

SCREENING FOR HEPATITIS C VIRUS INFECTION IN ADULTS
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adults aged 18 to 79 years
Recommendation	Screen for hepatitis C virus (HCV) infection. Grade: B

Risk Assessment	Although all adults aged 18 to 79 years should be screened, a number of risk factors increase risk. The most important risk factor for HCV infection is past or current injection drug use. In the US, recent increases in HCV incidence have predominantly been among young persons who inject drugs (PWID). Approximately one-third of PWID aged 18 to 30 years are infected with HCV, and 70% to 90% of older PWID are infected. Clinicians may want to consider screening in adolescents younger than 18 years and in adults older than 79 years who are at high risk (eg, past or current injection drug use). Pregnant adults should be screened. HCV prevalence has doubled in women aged 15 to 44 years from 2006 to 2014.From 2011 to 2014, 0.73% of pregnant women tested had an HCV infection, with a 68% increase in the proportion of infants born to HCV-infected mothers. Approximately 1700 infected infants are born annually to 29,000 HCV-infected mothers. Because of the increasing prevalence of HCV in women aged 15 to 44 years and in infants born to HCV-infected mothers, clinicians may want to consider screening pregnant persons younger than 18 years.
Screening Tests	Screening with HCV antibody testing followed by polymerase chain reaction testing for HCV RNA is accurate for identifying patients with chronic HCV infection. Currently, diagnostic evaluations are often performed with various noninvasive tests that have lower risk for harm than liver biopsy for diagnosing fibrosis stage or cirrhosis in persons who screen positive. Among patients with abnormal results on liver function tests (measurement of aspartate aminotransferase, alanine aminotransferase, or bilirubin levels) who were tested for reasons other than HCV screening, finding the cause of the abnormality often includes testing for HCV infection and is considered case finding rather than screening; therefore, it is outside the scope of this recommendation.
Screening Interval	Most adults need to be screened only once. Persons with continued risk for HCV infection (eg, PWID) should be screened periodically. There is limited information about the specific screening interval that should occur in persons who continue to be at risk for new HCV infection or how pregnancy changes the need for additional screening.
Treatment	Refer to http://hcvguidelines.org/ for the most up-to-date treatment recommendations.
Balance of Benefits and Harms	The US Preventive Services Task Force (USPSTF) concludes with moderate certainty that screening for HCV infection in adults aged 18 to 79 years has **substantial net benefit.**
Other Relevant USPTF Recommendations	The USPSTF has made recommendations on screening for hepatitis B virus infection in pregnant persons, screening for hepatitis B virus infection in adults, and screening for HIV infection.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statements, and supporting documents, please go to http://www.uspreventiveservicestaskforce.org/

Things to consider:

- Although the CDC recommends one-time testing for those between the ages of 18-79 of age, individuals outside of these age ranges should be considered for screening based on risk, exposure, and if treatment would benefit them.
- Vaccination against hepatitis A and hepatitis B are recommended for all susceptible persons with HCV infection.
- 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). Grade C. https://www.hcvguidelines.org/evaluate/testing-and-linkage
- For at risk HCV-seronegative individuals, HCV antibody testing is recommended annually or as indicated by risk exposure https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-c-virus-infection?view=full

USPTF and Implications of the Testing Recommendations

What is the US Preventive Services Taskforce?

The U.S. Preventive Services Task Force (USPSTF) is an independent panel of clinical experts established by Congress to evaluate and make recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms. USPSTF recommendations only address services offered in the primary care setting or services referred by a primary care clinician.

USPSTF MISSON

To improve health by making evidence-based recommendations about clinical preventive services such as:

- Screenings
- Counseling services
- Preventive medicine

The USPSTF grades recommendations based on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF assessment does not consider service provision costs. The table below summarizes the USPSTF grades and their implication for clinical practice.

A grade of 'A' indicates that the evidence suggests with a high degree of certainty that the recommendation is of substantial net benefit and USPSTF recommends providing the services. A grade of 'B' indicates that the evidence suggests with a high degree of certainty that the recommendation is of moderate net benefit or with a moderate degree of certainty that the recommendation is of moderate to substantial net benefit. The USPSTF recommends providing 'B' grade services.

USPSTF Grades Definitions & Suggestions for Practice

Grade	Definition	Suggestion for Practice
A	Recommended	Offer/provide the service.
B	Recommended	Offer/provide the service.
C	Recommended depending on patient situation	Offer/provide the service for selected patients depending on individual circumstances.
D	Not recommended	Discourage the use of the service.
I	There is not enough evidence to make a recommendation	Review the clinical considerations of the service in the USPSTF statement. If the service is offered, patients should understand about the balance of benefit and harm.

A grade of 'C' indicates that the evidence suggests with moderate certainty that the net benefit is small; therefore, the USPSTF recommends selectively offering the service to individual patients based on professional judgment and patient preferences. A grade of 'D' indicates that the evidence suggests with a moderate or high degree of certainty that the service has no net benefit or that the harms outweigh the benefits and the USPSTF recommends against the service. A grade of 'I' indicates that the evidence is insufficient to assess the balance of benefits and harms. Evidence may be lacking, of poor quality or conflicting. If the services are offered, it is important that the patient understand the uncertainty about the balance of benefits and harms.

USPSTF Level of Certainty Regarding Net Benefit	
Level of Certainty	Description
High	Available evidence includes consistent results from well-designed, well-conducted studies in representative primary care populations that assess the effects of the preventive service on health outcomes. Conclusions are unlikely to be affected by future studies.
Moderate	Available evidence is sufficient to determine effects of the preventive service on health outcomes, but confidence is limited. As more information becomes available, the observed effects could change and alter conclusions.
Low	Available evidence is insufficient to assess effects on health outcomes.

What are the Implications of USPSTF Recommendations?

1. The Patient Protection and Affordable Care Act (ACA) requires non-grandfathered, private health plans to cover clinical preventive services given a grade A or B by the USPSTF without cost sharing. It also provides incentives for Medicaid programs to cover these services.

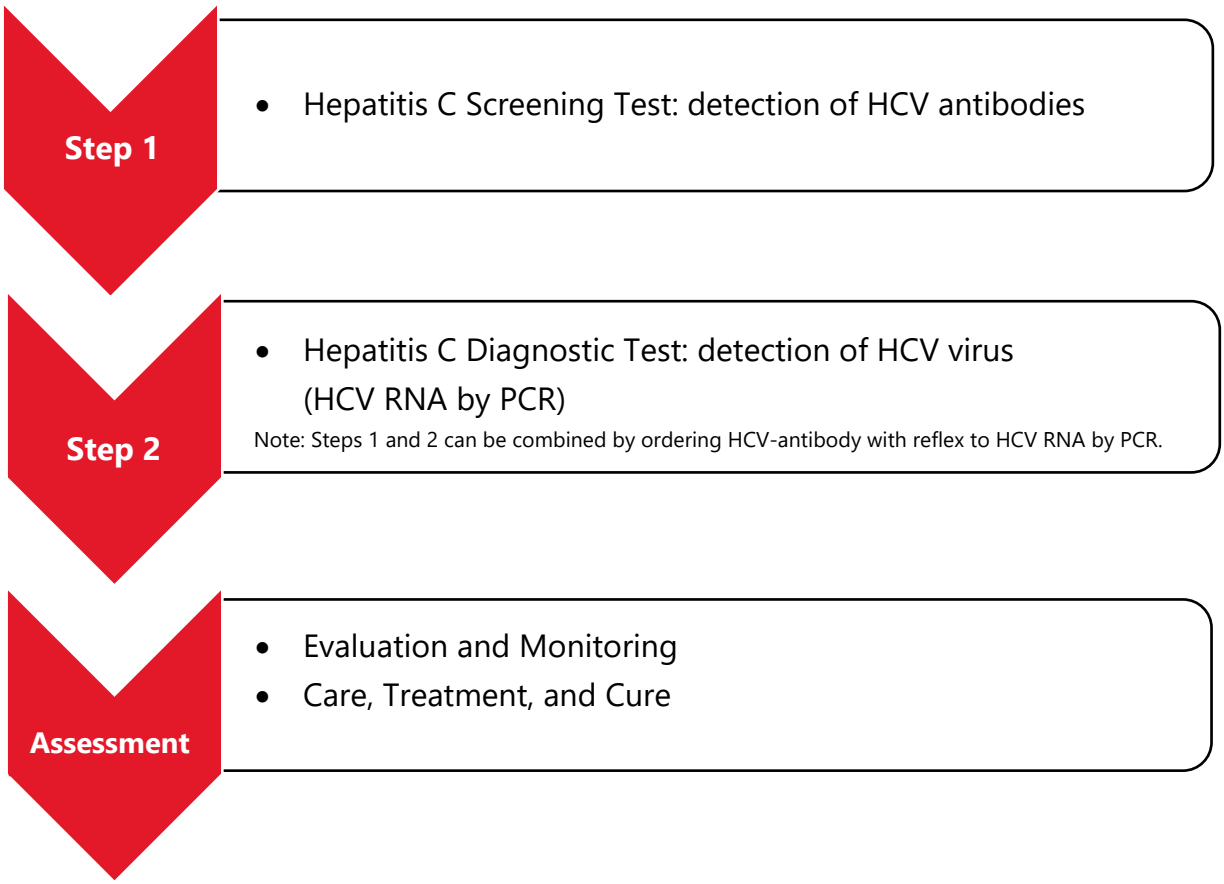
2. ACA prohibits insurance companies from declining to sell or renew policies because of preexisting conditions such as chronic HCV infection.

3. The Center for Medicare and Medicaid Services (CMS) is allowed to add coverage of "additional preventive services" if certain statutory requirements are met including a grade 'A' or 'B' recommendation by the US Preventive Services Taskforce.

Overview of Hepatitis C Screening, Diagnosis and Referral

Testing for hepatitis C infection is a **two-step process**, involving an initial hepatitis C screening test, which detects hepatitis C antibodies in the blood, followed by a hepatitis C diagnostic test (HCV RNA by PCR), which detects the presence of hepatitis C virus (HCV) in the blood. See Sections 8 and 9 for an overview of a CDC recommended testing sequence for identifying current hepatitis C virus infection and interpretation of test results.

Primary care providers can play an important role in each of these steps: promoting the initial offer to screen, reinforcing the importance of obtaining a diagnostic test, and assisting in preparing the patient for follow-up care and possible treatment.



Hepatitis C Screening Test: detection of HCV antibodies

Initial testing for HCV infection should begin with an FDA approved test for HCV antibody, either a rapid or a laboratory conducted assay for HCV antibody. Tests are reported as reactive or nonreactive. HCV infection can be detected by HCV antibody screening tests (enzyme immunoassay) 4-10 weeks after infection. HCV antibody can be detected in more than 97% of persons 6 months after exposure.

- A **nonreactive** HCV antibody result indicated that no HCV antibody detected. No further testing is needed unless there is suspicion of recent exposure. **NOTE**: If the person is immunocompromised, testing for HCV RNA may be considered.
- A **reactive** HCV antibody result indicates one of the following: 1) current HCV infection; 2) past HCV infection that has resolved; or 3) false positivity, meaning the person was never infected. A **reactive** HCV antibody result should be followed by testing for HCV viremia using nucleic acid testing for HCV RNA in order to confirm current/active hepatitis C infection. Patients should presume they are infected until they have the hepatitis C diagnostic testing done.

Hepatitis C Diagnostic Test: detection of HCV virus

A reactive HCV antibody test result should be followed by an FDA-approved nucleic acid test assay intended for detection of HCV RNA in serum or plasma from blood of at-risk patient. Either quantitative or qualitative HCV RNA tests can be used to confirm active infection.

- If HCV RNA is **detected**, results indicate current HCV infection.
- If HCV RNA is **not detected**, results indicate either past, resolved infection, cured infection, or false HCV antibody positivity.

Regardless of serology for HCV antibody, patients with detectable HCV RNA should be considered to have active HCV infection and should receive further medical evaluation. For patients with cured infection, assessment for HCV recurrence is recommended only if the patient develops unexplained hepatic dysfunction, or annual assessment if the patient has ongoing risk factors for HCV infection. In such cases, a quantitative HCV RNA test is recommended to assess HCV recurrence.

Refer to Section 5, "Interpretation of Results of Tests for Hepatitis C Virus Infection and Further Actions," for additional information.

Recommendations for Initial HCV Testing and Follow-Up

CDC recommends that all persons for whom HCV screening is recommended should initially be tested for HCV antibody using an assay approved by the US Food and Drug Administration.

- HCV antibody testing with reflex HCV RNA polymerase chain reaction (PCR) testing is recommended for initial HCV testing.
- 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.
- Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, HCV RNA testing is recommended because a positive HCV antibody test is expected.
- Quantitative HCV RNA testing is recommended prior to initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).
- HCV genotype testing may be considered for those in whom it may alter treatment recommendations.
- 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.

Counseling Messages for Screening Test Results

All patients should be provided information on the meaning of their test results:

For a non-reactive hepatitis C screening test:

- Explain the meaning of the non-reactive antibody test, ensuring that the patient understands a negative antibody test does not protect him/her from future infection in the event of risk-taking behaviors.
- Discuss that if the patient was recently exposed (6 months), they may be in a window period and recommend repeat screening in 6 months, and provide information on hepatitis C prevention, risk and harm reduction.
- Encourage the patient to make healthy choices and to get vaccinated against hepatitis A and B, if appropriate.

For a reactive hepatitis C screening test:

- Explain the meaning of the reactive antibody test and counsel on the need for diagnostic testing (hepatitis C RNA test) to confirm a diagnosis of chronic hepatitis C.
- Explain that the patient is possibly chronically infected and provide basic hepatitis C disease and treatment information.

- Educate patients that available oral therapies have over 90% cure rate.
- Discuss the importance of minimizing risk behaviors to avoid transmitting hepatitis C infection to others and encourage notification and screening of needle sharing and sexual partners.
- Discuss healthy liver practices, including stopping or reducing alcohol intake.
- Encourage the patient to make these healthy choices, describe the importance of regular medical care, and get vaccinated against hepatitis A and B, if immunity is not indicated by laboratory testing.

For those with an active infection:

- Persons with current HCV infection should receive education and interventions aimed at reducing liver disease progression and preventing HCV transmission.
- Abstain from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.
- Evaluation for other conditions that may accelerate liver fibrosis, including hepatitis B and HIV infections, is recommended for all persons with active HCV infection.
- Evaluation for advanced fibrosis using noninvasive tests (serum panels, elastography) or liver biopsy, if required, is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy, and to determine the need for initiating additional measures for cirrhosis management (eg, hepatocellular carcinoma screening).
- Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.
- Vaccination against pneumococcal, influenza, and COVID infection is recommended for all patients with cirrhosis.
- Provide education about how to prevent HCV transmission to others.

Management of Persons with Hepatitis C Infection

CDC recommends that all persons identified with HCV infection should receive:

- A brief alcohol screening and intervention as clinically indicated; and
- Assessment for appropriate care and treatment services for HCV infection.

While patients identified with chronic hepatitis C infection should be referred to a primary-care physician in treating hepatitis C, there is often a delay before the patient can be seen. Primary care providers can play a crucial role in delivering care and helping prepare patients for treatment, if appropriate.

Common Barriers to and Misconceptions Regarding HCV Treatment and Potential Strategies

Barrier	Strategy
Comorbid conditions (eg, substance use, psychiatric disorders, uncontrolled chronic medical conditions)	• Conduct counseling and education. • Refer for services (e.g., mental health services, medications for opioid use disorder [MOUDs], and syringe service programs). • Co-localize services (e.g., primary care, medical homes, and drug treatment).
Competing priorities and loss to follow-up	• Conduct counseling and education. • Engage case managers and patient navigators. Consider other strategies such as incentives, peer navigators, and transportation assistance. • Co-localize services (e.g., primary care, medical homes, and drug treatment).
Lack of access to treatment (eg, out-of-pocket costs, high copays, lack of insurance, geographic distance, and/or lack of specialist availability)	• Leverage expansion of coverage through the Patient Protection and Affordable Care Act. • Participate in models of care involving close collaboration between primary care clinicians and specialists. • Liaise with pharmaceutical patient assistance programs and copay assistance programs. • Co-localize services (e.g., primary care, medical homes, and drug treatment).

Lack of practitioner expertise	• Collaborate with specialists (e.g., project ECHO-like models and telemedicine). https://dph.georgia.gov/dph-viral-hepatitis-echo • Develop accessible, clear HCV treatment guidelines. • Develop electronic health record performance measures and clinical decision support tools (e.g., pop-up reminders and standing orders).

Laboratory tests	
Liver Health/HCV-related Assessments	Basic Health Assessments
- ALT, AST, total and direct bilirubin, albumin - Prothrombin time, including INR - HAV and HBV - Quantitative HCV RNA, HCV genotype	- CBC - Creatinine and GFR - Glucose or hemoglobin A1c - HIV
Management	
Patient Counseling	Clinical Management
- Preventing HCV transmission - HCV antibodies do not provide immunity - Avoid alcohol - Refer for substance use disorder treatment, if appropriate. Provide education on proper cleaning of equipment and sharing of needles and other drug equipment. - Avoid new medicines, including over-the counter and herbal agents, without first checking with their healthcare provider - Maintain a healthy diet and lose weight if necessary - Sources of support (e.g., social, emotional, financial)	- HAV and HBV vaccinations - Comorbidity management (depression, diabetes, and hypertension) - Medication assessment (for any products that may harm the liver)

AASLD Practice Guidelines

For the most updated recommendations on testing, management, and treatment of hepatitis C, please visit http://www.hcvguidelines.org.

Interpretation of Results of Tests for Hepatitis C Virus (HCV) Infection and Further Actions

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

TEST OUTCOME	INTERPRETATION	FURTHER ACTIONS
HCV antibody nonreactive	No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required. If recent exposure in person tested is suspected, test for HCV RNA.*
HCV antibody reactive	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection	Provide person tested with appropriate counseling and link person tested to care and treatment.†
HCV antibody reactive, HCV RNA not detected	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations,§ follow up with HCV RNA testing and appropriate counseling.

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

§ If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

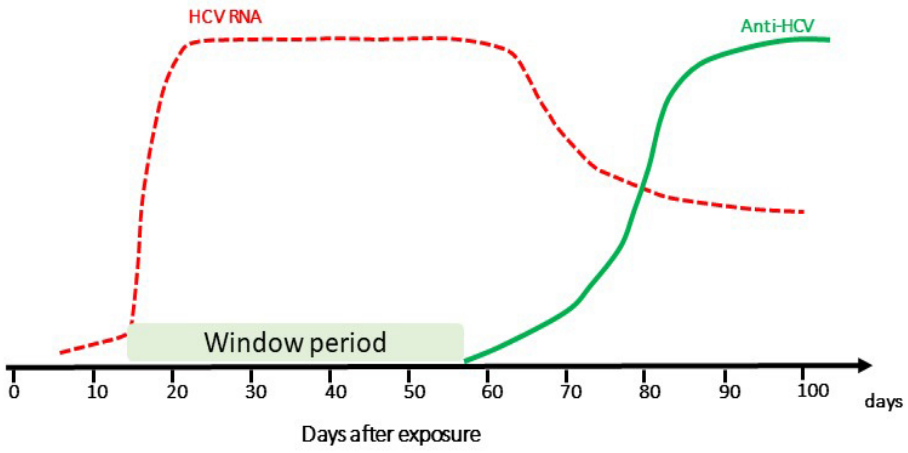
Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories

LABORATORY MARKERS OF HCV INFECTION

Currently available Hepatitis C Virus (HCV) antibody tests have a window period from exposure to HCV to detection of antibody of approximately 8-11 weeks. Nucleic acid amplification tests (NAT) can detect HCV RNA approximately 1-2 weeks after exposure. This means that for the first eight weeks following exposure to HCV antibody tests may not be able to detect HCV antibodies, and for the first 1-2 weeks following HCV exposure NATs may not be able to detect HCV RNA.

Figure 1: Laboratory Markers of HCV Infection (provided by S. Kamili, DVH, CDC)



ALL HCV ANTIBODY POSITIVE RESULTS REQUIRE SUPPLEMENTAL RNA TESTING

Since 2013, the US Centers for Disease Control and Prevention (CDC) recommends that all specimens that are HCV antibody reactive should be tested using a NAT to detect HCV RNA in order to confirm current HCV infection. To ensure all patients receive the recommended testing, the preferred practice is for laboratories to reflex all HCV antibody reactive specimens directly to NAT for HCV RNA. The 2013 recommendations supersede previous recommendations to report anti-HCV positive results only after applying assay-specific signal-to-cutoff (S/CO) thresholds or confirmation with the Recombinant ImmunoBlot Assay (RIBA), which is no longer available. S/CO ratios for HCV antibody testing are no longer recommended for:

1. determining which samples require additional testing
2. reporting of results to either healthcare providers or health department surveillance programs.

While reporting S/CO is not recommended, some health departments may still require reporting of S/CO and laboratories should confirm reporting requirements with the jurisdictional health department. However, all HCV antibody-reactive results should be followed with HCV RNA testing, irrespective of the local jurisdiction's reporting requirements.

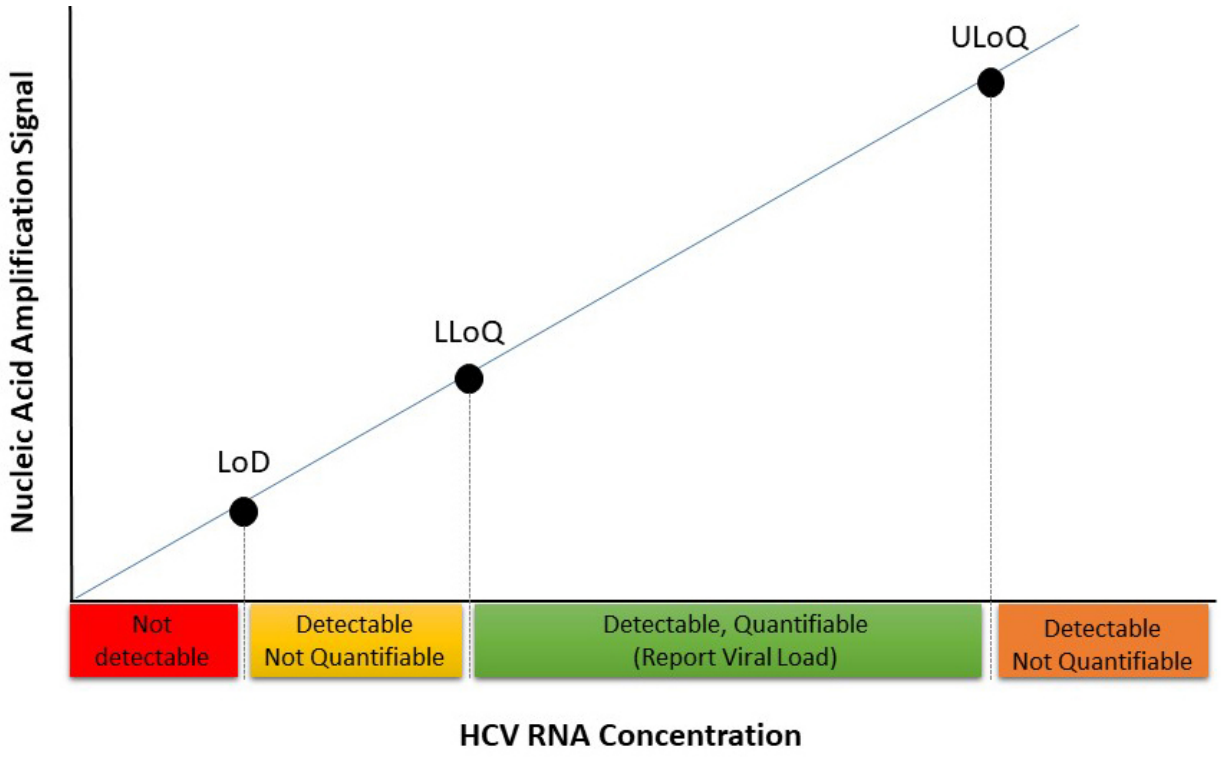
REPORTING "DETECTABLE NOT QUANTIFIABLE" RESULTS

Quantitative NATs measure the amount of viral nucleic acid (RNA or DNA) in the blood. Each FDA-approved NAT for quantitation of HCV RNA has a limit of detection (LoD), a lower limit of quantitation (LLoQ), and an upper limit of quantitation (ULoQ) (Figure 2, Table 1). All of these measures can vary by assay. Please refer to the package insert for the specific values and reporting language that applies to each assay. For your convenience, we have summarized the commonly used assays and values in Table 1 but the most updated information should be obtained from the manufacturer.

- The LoD represents the lowest concentration that HCV RNA can be detected
- The LLoQ represents the lowest concentration that HCV RNA can be accurately quantified

For some quantitative HCV RNA assays, the LoD and LLoQ are the same concentration. For others, the LLoQ is a higher concentration than the LoD and it is possible for the assay to detect HCV RNA but not quantify the amount present in the specimen. When the concentration of HCV RNA detected in a sample is above the LoD and below the LLoQ, the result is detectable but not quantifiable (Figure 2 (Yellow Box), Table 1,). The appropriate language to report this result varies by assay and is available in the package insert. **Reporting this result as HCV RNA negative or not detectable is inaccurate and misleading.** Provision of accurate results is essential to preventing transmission of the virus and to support clinical management.

Figure 2: LoD, LLoQ and ULoQ Related to HCV RNA Concentration



BEST PRACTICES FOR REPEAT HCV TESTING

There are certain scenarios where repeat HCV testing should be considered per CDC recommendations and the American Association for the Study of Liver Diseases in collaboration with the Infectious Disease Society of America.

- For persons who had a **negative HCV antibody result and a potential HCV exposure within the past six months**, testing for HCV RNA or follow-up testing for HCV antibody is recommended.
- For persons who had a **negative HCV antibody result and are immunocompromised or have liver disease**, testing for HCV RNA can be considered.

- For persons with a **positive HCV antibody result and negative HCV RNA result**, HCV RNA testing should be repeated if:
    - a potential HCV exposure occurred within the past six months.
    - clinical evidence of HCV infection is present.
    - there are concerns regarding specimen integrity including handling and storage conditions that may have compromised test results.
- For persons with a **positive HCV antibody result and a HCV RNA result that is detectable but too low to be quantified** repeat HCV RNA testing should be considered.
    - A low-positive HCV RNA result may occur for a number of reasons and collection of a follow-up specimen in 2-4 weeks for repeat testing should be considered.

Table 1: Currently Available FDA-Approved HCV Qualitative and Quantitative RNA Tests

Manufacturer (PMA #)	Device[a]	LoD[b] Serum	LoD[b] Plasma	LLoQ[c] (serum or plasma)	ULoQ[d] (serum or plasma)
Abbott Molecular (P00017)	Abbott RealTime HCV	1.08 $\log_{10}$ IU/mL **12.0 IU/mL**	1.08 $\log_{10}$ IU/mL **12.0 IU/mL**	1.08 $\log_{10}$ IU/mL **12.0 IU/mL**	8 $\log_{10}$ IU/ml **100,000,000 IU/mL**
Hologic (P020011)	Aptima HCV Qual Dx Assay	**5.3 IU/mL**	**5.3 IU/mL**	N/A Qualitative Assay	N/A Qualitative Assay
Hologic (P160023)	Aptima HCV Quant Dx Assay	0.53 $\log_{10}$ IU/mL **3.4 IU/mL**	0.59 $\log_{10}$ IU/mL **3.9 IU/mL**	1.0 $\log_{10}$ IU/ml **10.0 IU/mL**	8 $\log_{10}$ IU/ml **100,000,000 IU/mL**
Roche Molecular (P150015)	cobas-HCV (for 6800/8800)	**13.7 IU/mL**	**12.0 IU/mL**	**15.0 IU/mL**	**100,000,000 IU/mL**
Roche Molecular (P060030)[e]	COBAS Ampliprep/ COBAS Taqman HCV Test	**15.0 IU/mL**	**15.0 IU/mL**	**15.0 IU/mL**	**100,000,000 IU/mL**

a. Package Inserts are provided for reference use only. For the most updated version please either login to your account with the manufacturer, review the package insert with the assay that was included with the version that is currently being run, or contact a sales representative.

b LoD as assessed with the WHO international standard for HCV RNA (Genotype 1a); LoDs can vary for other HCV genotypes.

c. Roche Molecular uses the term Titer Min instead of Lower limit of Quantification

d. Roche Molecular uses the term Titer Max instead of Upper Limit of Quantification

e. P060030 was originally approved on 10/30/2008 for the quantitation of HCV RNA in patients undergoing anti-HCV treatment; the diagnostic claim was validated and submitted to FDA as a PMA supplement and was approved on 02/18/2016.

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Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.

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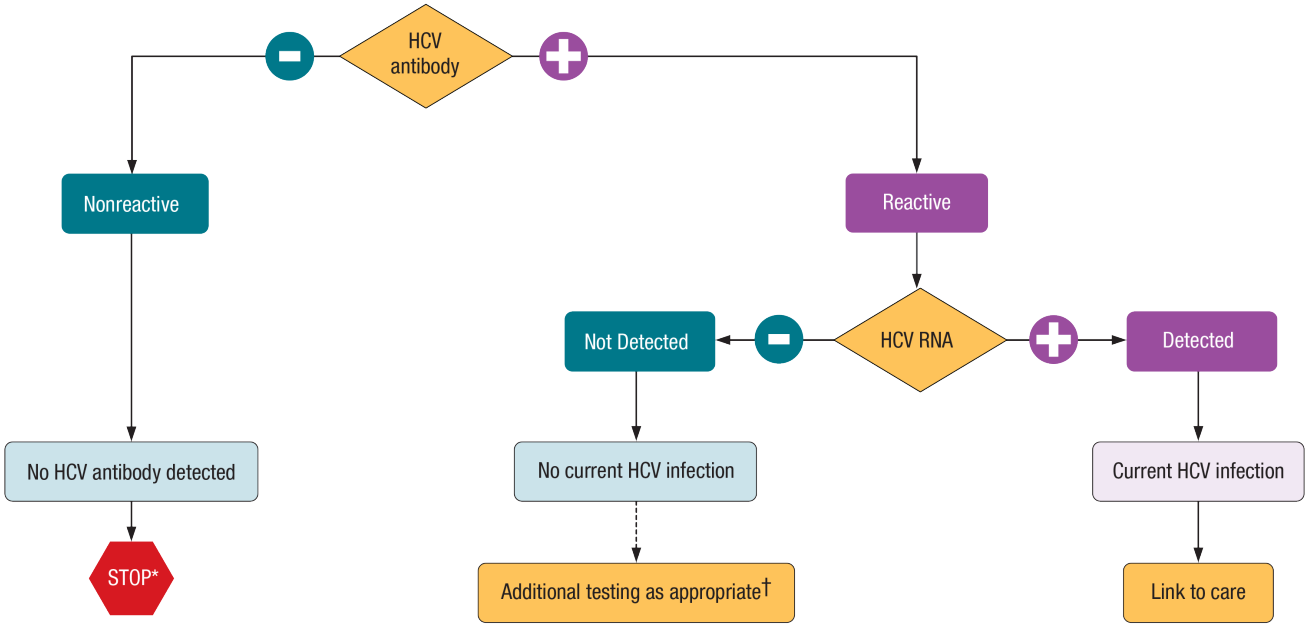
Testing For Hepatitis C Viral Infections:

FREQUENTLY ASKED QUESTIONS

In May 2013, the Centers for Disease Control and Prevention released Testing for HCV Infections: An Update of Guidance for Clinicians and Laboratorians. The updated guidelines emphasize identifying persons with current hepatitis C virus (HCV) infections and incorporate recent changes in the availability of certain commercial HCV antibody tests. The new recommended testing sequence includes an initial test with an FDA-approved test for HCV antibodies, followed by an FDA-approved diagnostic nucleic acid test (NAT) intended for the detection of HCV RNA in serum or plasma if the initial HCV antibody test is reactive (Figure 1). This document intends to provide answers to some frequently asked questions regarding the recommended testing sequence and outlines FDA-approved diagnostic HCV RNA tests (Table 1).

Figure 1: Recommended testing sequence for identifying current HCV infection[1]



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

1 http://www.cdc.gov/hepatitis/hcv/labtesting.htm

FREQUENTLY ASKED QUESTIONS

1. **Our laboratory's requisition specifies HCV antibody testing and HCV RNA testing as separate tests. Is the clinician required to order both types of tests in order for the laboratory to perform the full algorithm?** If the requisition specifies antibody testing only, it may be necessary for the clinician to order an HCV RNA test, as needed. A reflex option for an RNA test may be offered for positive antibody tests. Laboratories are encouraged to review their requisition process and consider revising the test menu to indicate HCV diagnostic testing without specifying the type of test.

2. **The new algorithm begins with an HCV antibody test. Can a rapid test that detects HCV antibodies be used for this step?** Yes, a test that has been approved by the FDA to screen for HCV antibodies for diagnostic purposes may be used for the HCV antibody test step at the beginning of the algorithm. This may be an FDA-approved HCV rapid test or a conventional HCV antibody immunoassay. If the laboratory receives an appropriate specimen from a patient who has already tested reactive on a rapid test, no additional testing to confirm antibodies is needed. A suitable specimen may be submitted directly for RNA testing to determine current infection status.

3. **In the past, laboratories were encouraged to report the signal-to-cutoff ratios from laboratory-based HCV enzyme immunoassays (IA). Should laboratories continue to report signal-to-cutoff ratios?** The signal-to-cutoff ratio is not needed to interpret results in the newly recommended testing sequence. However, package inserts for some HCV IAs may recommend reporting signal-to- cutoff ratios. For information on reporting the signal-to-cutoff ratio, refer to the package inserts of assays and consider your jurisdiction's individual surveillance needs. Note: An HCV RNA test is indicated when an HCV IA test is reactive, regardless of signal-to-cutoff ratio.

4. **The algorithm indicates that an HCV RNA test should be performed for all patients who have a reactive HCV antibody test result. Are laboratories allowed to reflex directly to the RNA test?** If the specimen submitted to the laboratory is acceptable for the HCV RNA test, the laboratory may reflex directly to the HCV RNA test. In some cases, a separate sample tube or a pristine aliquot may be submitted and processed for RNA testing if needed. If the original specimen is not suitable for RNA testing, or if insufficient volume remains, the laboratory should request another blood specimen and provide appropriate collection instructions. Laboratories may need to alter their requisition forms to include an option to specifically request an HCV RNA test or to reflex to HCV NAT following a positive antibody test according to the algorithm.

5. **Can a quantitative HCV RNA test (i.e. a viral load test) be used in the HCV RNA test step of the algorithm?** Currently, available HCV quantitative RNA tests are approved by FDA for the management of patients undergoing antiviral therapy and should only be performed after a confirmed diagnosis of active HCV. Quantitative HCV RNA tests are not intended for diagnostic use, and any use in the diagnostic algorithm would be off-label. To use a quantitative HCV RNA test in the diagnostic algorithm, the laboratory must have performed an appropriate validation study. Quantitative HCV RNA tests should only be used after the

validation is completed or if a physician has specifically ordered the test.

6. **If the laboratory performs HCV antibody testing on serum specimens, can the same serum specimen be used for the HCV RNA test step?** Laboratories must adhere to the specimen collection, processing and storage criteria for the RNA test as approved by the FDA. Specimens must be handled with care to minimize the chance of cross contamination. If serum is an acceptable specimen type listed in the package insert, then it may be used.

7. **What testing should be recommended if an individual has a reactive HCV antibody test, but the HCV RNA test is negative?** If the HCV antibody test is reactive, but HCV RNA is not detected, the laboratory should report the results with an interpretation of "HCV RNA not detected." The laboratory may recommend further actions that include re-testing with a different HCV antibody test, repeat testing if the person may have had a recent (within 6 months) exposure or has clinical evidence of HCV disease.

Table 1: FDA Approved Diagnostic HCV RNA Tests

	Test Name	Manufacturer	Intended Use	LOD/LLOQ	Specimen Type
Qualitative HCV RNA Tests	**VERSANT HCV RNA Qualitative Assay/APTIMA HCV RNA Qualitative Assay**	Gen-Probe	Diagnostic	7.5 IU/mL (genotype 1) 9.6 IU/mL overall	Serum or plasma (EDTA, sodium heparin, sodium citrate, and ACD)
	COBAS Amplicor HCV Test, v2.0 *and* **COBAS AmpliPrep/COBAS Amplicor HCV Test, v2.0**	Roche	Diagnostic	100 IU/mL	Serum or plasma (EDTA)
	AMPLICOR HCV Test, v2.0	Roche	Diagnostic	50 IU/ml	Serum or plasma (EDTA)
Quantitative HCV RNA Tests	**Abbott RealTime HCV**	Abbott	Aids in the management of HCV-infected patients undergoing antiviral therapy	12/12 IU/mL	Serum and plasma (EDTA)
	COBAS AmpliPrep/COBAS TaqMan HCV Test *and* **COBAS TaqMan HCV Test For Use With The High Pure System**	Roche	Aids in the management of HCV-infected patients undergoing antiviral therapy	15/15 IU/mL 20/25 IU/mL	Serum and plasma (EDTA)
	VERSANT HCV RNA 3.0 bDNA	Siemens	Aids in the management of HCV-infected patients undergoing antiviral therapy	LOD 988 (340 system) 1,100 IU/mL (440 system) Detection Cutoff 615 IU/mL	Serum and plasma (EDTA, ACD)

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Coding Guide for Viral Hepatitis Screening and Diagnosis

Coverage and actual dollar reimbursements often vary among insurers, as well as a patient's individual insurance plan. The actual reimbursement may also depend on whether or not the patient has met their annual deductible.

Below are some guidelines for seeking reimbursement for viral hepatitis screening and diagnosis. Appropriate Current Procedure Terminology (CPT) and International Classification of Diseases (ICD) codes are required for each claim submission for the performance of a hepatitis related test.

ICD-10 Diagnosis Codes	
Z20.5	Contact with / suspected exposure to viral hepatitis
Z20.828	Exposure to viral disease not elsewhere classified (NEC)
Z21	Asymptomatic human immunodeficiency virus (HIV) infection status
Z23	Encounter for prophylactic vaccination
Z72.51	High-risk sexual behavior, heterosexual
Z72.52	High-risk sexual behavior, homosexual
Z72.53	High-risk sexual behavior, bisexual
Z00.00	Routine medical examination of adult; Encounter for laboratory as part of general medical examination
Z00.01	Encounter for general medical examination of adult with abnormal finding
Z00.8	Encounter for other general examination
Z11.59	Encounter for screening for other viral disease
K74.0	Hepatic fibrosis
B17.10	Acute hepatitis C without hepatic coma
B18.2	Chronic hepatitis C without hepatic coma
B19.20	Unspecified viral hepatitis C without hepatic coma
B20	Human immunodeficiency virus (HIV) disease

B17.9	Acute viral hepatitis, unspecified
B19.9	Unspecified viral hepatitis without hepatic coma
Z86.19	History of hepatitis B; history of hepatitis C
O98.41	Pregnancy complicated by care of/management affected by viral hepatitis
Z72.89	Other problems related to lifestyle
F19.20	Other psychoactive substance abuse, uncomplicated
Z22.52	Carrier of viral hepatitis C

Viral Hepatitis CPT Codes	
Testing Codes	
86803	HCV antibody
G0472	HCV antibody screening for individual at high risk and other covered indication(s)
86804	HCV antibody; confirmatory test (e.g., immunoblot or RIBA)
87520	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique
87521	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, amplified probe technique
87522	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, quantification
87902	Infectious agent genotype analysis by nucleic acid (DNA or RNA); Hepatitis C virus
3266F	Hepatitis C, genotype test
82105	Alpha-fetoprotein (AFP); serum
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, intramuscular and jet injections), one vaccine (single or combination vaccine/toxoid)
90472	Each additional vaccine (single or combination vaccine) List separately in addition to the code for primary procedure
90632	Monovalent hepatitis A vaccine for adult dosage
90633	Monovalent hepatitis A vaccine for pediatric/adolescent use (2-dose schedule)
90634	Monovalent hepatitis A vaccine for pediatric/adolescent use (3-dose schedule)

90636	Combination hepatitis A/hepatitis B vaccine for adult dosage
90740	Hepatitis B vaccine for dialysis or immunosuppresses patient (3-dose schedule)
90743	Monovalent hepatitis B vaccine for adolescent use (2-dose schedule)
90745	Monovalent hepatitis B vaccine for pediatric use (3-dose schedule)
90746	Monovalent hepatitis B vaccine for adult dosage
90747	Hepatitis B vaccine for dialysis or immunosuppressed patient (for 40 mcg dosing and 4-dose schedule)
91299	Unlisted Diagnostic Gastroenterology Procedure. If physicians own the equipment and are performing the FibroScan in their office.
E & M Codes	
90201-99205	Office or outpatient visit for the evaluation or management of a new patient
99241-99275	Consultations: Office or other outpatient, initial or follow-up inpatient, and confirmatory
36415	Collection of venous blood by venipuncture

Referral for Hepatitis C Treatment Evaluation

Date of Referral: _____

Name of referring provider/facility: _____

Office Address: _____

Phone: _____ Fax: _____

Name of provider/facility patient is being referred to: _____

Office Address: _____

Phone: _____ Fax: _____

Patient Name: _____

Date of Birth: _____ Gender: _____

Address: _____

Home Phone Number: _____ Mobile Phone Number: _____

Patient's Preferred Language: _____ Does Patient Need an Interpreter? ☐ Yes ☐ No

Reason for Referral: _____

CONCOMITANT MEDICAL DIAGNOSIS	CURRENT MEDICATIONS

SUBSTANCE USE	
Use of alcohol: ☐ Yes ☐ No	If yes, indicate amount of use:
Substance use: ☐ Yes ☐ No	If yes, indicate substance:

If positive, patient may need substance abuse counseling prior to being considered for hepatitis C treatment.

RECOMMENDED LABORATORY TESTING PRIOR TO INITIAL APPOINTMENT WITH SPECIALIST					
HCV RNA	Date:	ALT	Date:	Creatinine	
HCV Genotype		AST	Date:	Platelet Count	
Albumin		Total bilirubin		Hemoglobin	
HIV Status*:	☐ Negative	☐ Positive: Stable or Unstable		PT/INR	
Pregnancy: ☐ Yes ☐ No					
Vaccine status: Hepatitis A: ☐ Yes ☐ No			Hepatitis B: ☐ Yes ☐ No		

**If HIV positive, refer to (or refer back to) Infectious Disease / HIV Specialist*

ASSESSMENT OF LIVER (Complete if Available)		
Test Performed:	Date	Findings/Results (may attach report)
Liver Biopsy or noninvasive test		
Ultrasound or Transient Elastography		

COMMENTS / OTHER RECOMMENDATIONS / REFERRALS

Fax to Hepatitis C Provider/Facility:

☐ Completed referral form ☐ Copy of patient's insurance card ☐ Medication list

☐ Pertinent test results ☐ Clinical notes

Educational Resources for Medical Providers

CDC Division of Viral Hepatitis:
The Division of Viral Hepatitis (DVH) is part of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention at CDC. In collaboration with domestic and global partners, DVH provides the scientific and programmatic foundation and leadership for the prevention and control of hepatitis virus infections and their manifestations.

DVH consists of three branches — the Epidemiology and Surveillance Branch, the Prevention Branch, and the Laboratory Branch — that work collaboratively to prevent viral hepatitis infections and associated liver disease.
www.cdc.gov/hepatitis

CDC Morbidity and Mortality Weekly Report (http://www.cdc.gov/mmwr/)
This weekly report provides updated information on specific diseases as reported by state and territorial health departments. It is a good source for updated CDC recommendations, reports and other items of interest to the public health community.

The following link provides a shortcut to all of the Morbidity and Mortality Weekly reports (MMWR) that relate directly to viral hepatitis.
http://www.cdc.gov/hepatitis/Resources/Professionals/MMWRs.htm

CDC Advisory Council on Immunization Practices
(http://www.cdc.gov/vaccines/acip/recs/index.html) develops written recommendations for the routine administration of vaccines to children and adults. A complete listing of these recommendations as well as the recommended immunization schedules can be found at the link below.

CDC Division of Viral Hepatitis, 2025 Strategic Plan
(https://www.cdc.gov/hepatitis/pdfs/DVH-StrategicPlan2020-2025.pdf)
The U.S. has the responsibility to eradicate viral hepatitis as a public health threat. The CDC's Division of Viral Hepatitis presented its 2025 strategies to reduce new viral hepatitis infections, reduce morbidity and mortality, viral-hepatitis related disparities, and establish comprehensive national viral hepatitis surveillance.

Action Plan for the Prevention, Care, & Treatment of Viral Hepatitis
(https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf?language=es)

The 2021-2025 update for the Action Plan for the Prevention, Care, & Treatment of Viral Hepatitis was released in January 2021. This Action Plan was developed across multiple Federal agencies, including the Department of Health and Human Services, Department of Justice, Department of Housing and Urban Development, and Veteran Affairs. This Action Plan aims to prevent new infections and improve the diagnosis, care, and treatment of those living with chronic hepatitis C in the U.S.

AASLD – IDSA Recommendations for Testing, Managing and Treating Hepatitis C (http://www.hcvguidelines.org/)
The Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management to provide healthcare professionals with timely guidance, as new therapies are available and integrated into HCV regimens. This Guidance should be considered a "living document" in that new sections will be added and updated frequently as new information and treatments become available.

Rx Assist Patient Assistance Program Center (https://www.rxassist.org/) offers a wide-ranging database of patient assistance programs as well as current news, articles, and tools so patients and health care professionals can find the information they need, all in one place.

HealthWell Foundation (https://www.healthwellfoundation.org/fund/hepatitis-c/) is a non-profit organization devoted to refining access to care for the uninsured. When health insurance is not enough to cover costs, the HealthWell Foundation will fill the gap by assisting with deductibles, copays, premiums, and out-of-pocket expenses.

Patient Advocate Foundation Co-Pay Relief Program (https://copays.org/funds/hepatitis-c/) provides direct compensation for deductibles, co-insurance, and co-pays for patients in need of monetary support. In some cases, assistance with insurance premiums and/or ancillary services associated with hepatitis C may also be available.

Hepatitis C Online (https://www.hepatitisc.uw.edu/) is a free educational website from the University of Washington National Hepatitis Training Center. This project is funded by the Centers for Disease Control and Prevention (CDC) and addresses the diagnosis, monitoring, and management of hepatitis C virus infection. Free CME credit and CNE/CE contact hours are offered throughout the site.

HEP Drug Interactions (https://www.hep-druginteractions.org/checker) provides a clinically useful, reliable, comprehensive, up-to-date, evidence-based drug-drug interaction resource, freely available to healthcare workers, patients, and researchers.

Patient Resources

Georgia Department of Public Health, Division of Viral Hepatitis: Georgia Viral Hepatitis Resource Directory (https://dph.georgia.gov/epidemiology/viral-hepatitis)

Centers for Disease Control and Prevention, Division of Viral Hepatitis: Patient Education Resources (http://www.cdc.gov/hepatitis/HCV/PatientEduHCV.htm)

> **CDC Know More Hepatitis**
> *Know More Hepatitis* is a joint project of the NCHHSTP and the CDC Foundation to increase awareness of viral hepatitis and promote screening for viral hepatitis. The site offers a wealth of materials to support community awareness, including an online risk assessment, fact sheets, buttons, badges, and posters.
> http://www.cdc.gov/KnowMoreHepatitis/ (Hepatitis C)
> http://www.cdc.gov/KnowHepatitisB/ (Hepatitis B)

American Liver Foundation (http://www.liverfoundation.org/)
This website provides information on liver diseases, advocacy for education, treatment and research funding.

Hepatitis C Caring Ambassadors (http://www.hepcchallenge.org/)
The Hepatitis C Caring Ambassadors Program mission is to improve the lives of people living with hepatitis C, through information and awareness.

Harm Reduction Coalition (http://www.harmreduction.org/)
The website offers a variety of tools and resources that reflect the most current and innovative information on methods for reducing drug related harm, including brochures, fact sheets, manuals, posters, training curricula, videos, bulletins, and podcasts that span all aspects of harm reduction.

Help 4 Hep (http://help4hep.org/) is a free helpline for those with concerns and questions about hepatitis C. The toll-free number for Help4Hep is 1**-877-Help-4-Hep** (1-877-435-7443)

Center Watch (http://www.centerwatch.com/) offers a state-by-state listing of clinical trials for viral hepatitis.

Patient Advocate Foundation Co-Pay Relief
(http://www.copays.org/diseases/hepatitis-c) is a patient assistance program that may be helpful for those in need of financial assistance for hepatitis C care and treatment.