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Hepatitis C Diagnostic Testing

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Module 1: Screening and Diagnosis of Hepatitis C Infection
Lesson 3: Hepatitis C Diagnostic Testing

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HCV Diagnostic Tests

Serologic Antibody Assays

Initial testing for the diagnosis of hepatitis C infection uses serologic assays that detect human antibodies generated as a response to hepatitis C virus (HCV) infection.[1,2,3] A positive HCV antibody test indicates one of the following three scenarios: (1) active infection, (2) past HCV infection that has resolved or been cured, or (3) a false-positive test.[1,4] None of these anti-HCV antibody tests can differentiate whether the infection is new (acute), chronic, or no longer present.

- **Enzyme Immunoassay (EIA)**: The third-generation HCV EIA detects antibodies that bind to recombinant antigens derived from four HCV regions: core, nonstructural 3, nonstructural 4, and nonstructural 5 (Figure 1).[6,7] The EIA test is reported as positive or negative based on an absorbance signal compared with a cutoff value.
    - Sensitivity of EIA and False-Negative Results: The third-generation HCV EIA has a sensitivity of approximately 98%.[8,9,10] Circumstances associated with a false-negative EIA include patients with acute HCV infection, persons with major immune compromising conditions (advanced HIV infection or organ transplantation recipients), and persons with chronic renal failure on long-term hemodialysis.
    - Specificity of EIA and False-Positive Results: The third-generation HCV EIA has a reported specificity greater than 99%; false-positive tests can occur with increased gamma globulin production, with autoimmune diseases, and following immunizations.[8] In addition, a false-positive test is more likely when performing widespread testing in populations that have a very low HCV prevalence.
- **Chemiluminescence Immunoassay (CIA)**: The CIA test is an antibody test similar to the EIA but is used less frequently than the EIA test. For the diagnosis of HCV, the CIA has similar sensitivity and specificity as the third-generation EIA.[1,11]
- **Point-of-Care Rapid Immunoassays**: The OraQuick HCV Rapid Antibody Test was approved by the U.S. Food and Drug Administration (FDA) in 2010 as a point-of-care test for use with whole blood samples obtained by either venipuncture or fingerstick. This OraQuick Rapid Antibody Test can be used as an alternative to the third-generation EIA for initial HCV antibody testing.[12,13,14,15] The OraQuick test is read 20 to 40 minutes after the test device is inserted into the buffer, and the result is either reactive or nonreactive (Figure 2).[12,13] In 2011, the FDA granted a Clinical Laboratory Improvement Amendments (CLIA) waiver for the OraQuick HCV Rapid Antibody Test. Additional point-of-care rapid HCV antibody tests have been developed but are not approved for use in the United States.[16,17]

Molecular HCV RNA Tests

Molecular diagnostic tests for hepatitis C specifically detect HCV RNA and the process is commonly referred to as a Nucleic Acid Test (NAT) or Nucleic Acid Amplification Test (NAAT).[18] The HCV NAT becomes positive approximately 1 to 2 weeks after initial HCV infection.[19] The NAT test has become the gold standard supplemental test for patients who have a positive HCV EIA screening test.[2,18] The NAT can determine whether a patient with a positive HCV antibody test has current (active) or resolved HCV infection.[2,6] In addition, the NAT can be used in combination with other laboratory studies, such as prior antibody test results or hepatic aminotransferase levels, to suggest the possibility of acute HCV infection.[19] The results for the commercially available quantitative HCV RNA assays, which were previously reported as copies/mL, are now given in International Units per milliliter (IUs/mL).[6]

- **Qualitative HCV RNA**: The qualitative HCV RNA tests provide a *yes* or *no* answer to whether detectable HCV RNA is present in the patient's blood sample.[20] The qualitative HCV RNA assays are FDA-approved for HCV diagnostic purposes. These tests, however, do not provide a quantitative level of HCV and are not used for baseline HCV RNA levels or for monitoring response to therapy.[20] For most qualitative HCV RNA assays, the lower limit of detection is 10-15 IU/mL.[20]
- **Quantitative HCV RNA**: The quantitative HCV RNA tests detect and quantify the number of HCV copies in the patient's blood sample, reported as IU/mL. Clinically, these tests are used for diagnosing HCV and monitoring response to therapy. Quantitative HCV RNA tests used for diagnosis and monitoring should have a lower limit of detection of 25 IU/mL or less.[6,21]

Immunoassays for HCV Core Antigen

As an HCV diagnostic marker, HCV core antigen has been studied, either alone or as an HCV antibody-HCV antigen combination assay.[22,23] Some experts have proposed the use of an HCV core antigen test as a less expensive option than HCV RNA testing, but there are no HCV antigen assays (or HCV antigen-antibody combination assays) that are FDA-approved for use in the United States at this time.[24,25]

HCV Testing Sequence

Recommended Testing Sequence

In May 2013, the Centers for Disease Control and Prevention (CDC) published a recommended testing sequence for diagnosing current (active) hepatitis C infection (Figure 3).[2] This 2013 HCV diagnostic testing sequence recommended by the CDC is not intended for the diagnosis of acute HCV infection.[2] The 2013 recommended testing sequence consists of initial HCV antibody testing (using either a rapid or laboratory-conducted assay), followed by HCV RNA testing for all persons with a positive HCV antibody test.[2] Using this algorithm, the following test results are possible.[2]

- **Negative HCV Antibody Test**: Persons who have a negative screening HCV antibody test are considered not infected with HCV and do not need further diagnostic evaluation, unless they have a known risk factor for a false-negative test, such as suspected acute HCV infection, chronic hemodialysis, or an immunocompromising condition, such as HIV infection with a low CD4 cell count.
- **Positive HCV Antibody and Positive HCV RNA**: Individuals who have a positive HCV antibody test and a positive HCV RNA are considered to have current (active) HCV infection.
- **Positive HCV Antibody and Negative HCV RNA**: Individuals with a positive HCV antibody test and a negative HCV RNA assay have evidence of prior exposure to HCV but do not have current HCV infection. This testing profile occurs in the setting of spontaneous clearance of HCV or successful treatment.

Reflexive HCV RNA Testing with Positive Initial HCV EIA

The CDC encourages setting up a procedure whereby samples that test positive with a laboratory-conducted HCV antibody assay will then undergo reflexive HCV RNA testing using the same patient's blood sample.[26] Many laboratories now offer reflexive HCV RNA testing on HCV antibody-positive samples.[2] The reflexive testing approach is more efficient than other approaches for follow-up HCV RNA testing that include (1) collecting two separate venipuncture samples at the initial blood draw (with the option of ordering the HCV RNA test if the antibody test is positive) or (2) having the patient return for another venipuncture after receiving a positive antibody test result.[2] From a practical standpoint, it is clearly preferable to have the laboratory reflexively perform the HCV RNA testing for positive HCV EIA tests utilizing the same blood sample.

Interpreting and Communicating Test Results

Interpretation of HCV Test Results and Recommended Action

Prior to discussing the HCV test results with the individual who has undergone testing, it is important to interpret the test results and have a plan for communicating the test results and your recommended further action (Table 1).[2] Individuals who engage in activities, such as injection drug use, that place them at higher risk of acquiring HCV should undergo regular screening for HCV infection.

Negative HCV Antibody

Individuals with a negative HCV antibody test result should be informed they are not infected with HCV, as long as they have not had a potential exposure to HCV in the prior 6 months.[2] If they have not had a potential exposure to HCV in the prior 6 months, they do not need further follow-up HCV testing, unless they have an exposure to HCV in the future or engage in activities that place them at ongoing risk for HCV acquisition.[2]

Negative HCV Antibody and Positive HCV RNA

Individuals who have a negative HCV antibody test in the setting of a recent exposure to HCV may possibly have acute or very early HCV infection. In this situation, an HCV RNA test should be ordered and, if positive, would indicate acute or very early HCV infection. Given the potential fluctuations of HCV RNA levels early after infection, a follow-up HCV RNA level is indicated for individuals with a recent (within 6 months) exposure to HCV if the HCV RNA is negative.

Positive HCV Antibody and Negative HCV RNA

Individuals with a positive HCV antibody test and a negative HCV RNA should be informed they do not have evidence of current hepatitis C infection.[2] It should be explained to the patient that most likely they were previously infected with HCV, but cleared the infection on their own. In addition, persons who have been successfully treated for HCV will also have a positive HCV antibody and negative HCV RNA. In both of these situations, they do not need further follow-up HCV testing if they do not subsequently have exposure to HCV. If, however, they have ongoing or future risk for reacquiring HCV, future testing for active HCV infection should be performed with a repeat HCV RNA, as the HCV antibody test will remain reactive for life. Individuals who have a positive HCV antibody and negative HCV RNA should receive counseling that prior infection does not make them immune to reinfection with HCV.[27,28,29]

Positive HCV Antibody and Positive HCV RNA

Individuals with a positive HCV antibody and positive HCV RNA should be told they have active hepatitis C infection, and they should clearly understand they need medical follow-up evaluation and treatment for HCV.[2] A single positive HCV RNA value indicates infection but must be interpreted in the context of clinical history to determine whether the individual has acute or chronic infection. For persons with a positive HCV antibody and positive HCV RNA, the CDC has generated counseling messages that focus on four areas: (1) contacting a health care provider for further evaluation and management of their HCV infection, (2) protecting their liver from further harm, (3) addressing weight management in overweight and obese persons, and (4) minimizing transmission of their HCV to others (Table 2).[30] In addition, the CDC recommends performing alcohol screening and brief intervention, which consists of screening for excessive alcohol consumption, brief counseling for individuals who screen positive, and referral to a specialized alcohol treatment program for individuals with possible alcohol dependence.[30]

Linkage to Care

Recommendations Regarding Linkage to Care

All persons identified with active hepatitis C infection (positive HCV RNA) should be linked to a medical provider who can provide competent and comprehensive management of HCV.[21,30] Available data suggest that in the current era, nonspecialists can effectively manage HCV, especially with backup and consultation for more complicated issues.[31,32,33,34,35] The management of patients with decompensated cirrhosis should always involve a hepatologist. In addition, persons with HCV who have prior treatment experience, hepatitis B coinfection, hepatocellular carcinoma, prior liver transplantation, or extrahepatic complications of HCV infection will likely require referral to a specialist. An individual with a positive HCV antibody test but negative HCV RNA level does not require a referral for further evaluation and management of HCV infection.

Recommended Laboratory Evaluation Prior to Referral

All persons referred for further evaluation and management of HCV infection should have a confirmed positive HCV RNA level, preferably a quantitative HCV RNA level (viral load) and not a qualitative HCV RNA level.[21] It is ideal, but not imperative, that the clinician who makes the diagnosis of HCV infection can perform some preliminary tests to provide advanced information in anticipation of the initial referral visit. These initial preliminary tests include tests of synthetic liver function (platelet count, total bilirubin, albumin, prothrombin time [PT]), hepatic inflammation (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and assays to detect relevant coinfection—HIV antibody, hepatitis A antibody, hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and total antibody to hepatitis B core antigen (anti-HBc).[21] For primary care medical providers who are taking on a more comprehensive role for the initial evaluation and management, see Module 2, Lesson 1 for a detailed discussion in the Core Concept Initial Evaluation of Persons with Chronic Hepatitis C.

Gap in Linkage to Care

Unfortunately, many individuals diagnosed with HCV infection (positive HCV RNA) do not get linked to appropriate care for their HCV infection.[36] Multiple reasons for gaps in linkage to care have been cited, including failure of the medical provider to make the referral, lack of medical insurance, substance use, mental health disorders, and housing instability that interfere with making or keeping referral appointments. Linkage to care rates have been lower among racial and ethnic minorities. Failure to link to care negatively impacts health outcomes in persons living with HCV infection.[37] With highly effective HCV treatment now available for all HCV genotypes, referral for evaluation and management of HCV has taken on even greater importance.

Strategies for Improving Linkage to Care

Attempts at the public health level to implement an HCV testing and linkage-to-care program have shown that additional funds can be used to leverage existing programs and provider networks.[38,39] The CDC and other organizations are actively working to explore strategies, such as the Hepatitis Testing and Linkage to Care (HepTLC) initiative, to enhance linkage to care for persons with HCV infection, including through simplification and decentralization of treatment.[40,41] Some individuals face barriers that prevent them from linking to care and receiving HCV treatment. For more information on this topic, see Module 4, Lesson 3: Addressing Structural Barriers to HCV Treatment.

Summary Points

- Diagnostic tests for hepatitis C include serologic assays that measure human antibodies generated in response to HCV infection and molecular virologic assays that directly detect HCV RNA.
- The third-generation HCV EIA test is the most frequently used antibody test to initially screen for HCV infection. The test has high sensitivity and specificity, but does not distinguish between current and resolved hepatitis C infection.
- The OraQuick HCV Rapid Antibody Test is available as a point-of-care rapid test and can be used for initial HCV antibody screening.
- Quantitative HCV RNA assays are the preferred supplemental test for persons who have a positive screening HCV antibody test. Testing positive for HCV RNA indicates current (active) HCV infection. Qualitative HCV RNA assays can be used for diagnosis but do not offer any advantage over the quantitative assay and should not be used for monitoring response to treatment.
- The 2013 CDC-recommended testing sequence for identifying current HCV infection consists of initial HCV antibody testing (either rapid or laboratory-conducted assay) followed by an HCV RNA assay for all positive antibody tests.
- All HCV testing results should be communicated to the person undergoing testing; individuals who have a positive HCV RNA assay should understand they have current (active) hepatitis C infection.
- Individuals who have a positive HCV RNA assay and newly diagnosed hepatitis C should receive preliminary counseling about protecting their liver from further harm, including cessation of alcohol use, strategies for weight loss if they are overweight, and how to minimize their risk of transmitting HCV to others.
- Individuals with newly diagnosed hepatitis C infection should be linked to clinical care for further liver disease evaluation and HCV treatment.

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Figures

Figure 1 HCV Third-Generation EIA Test

The third-generation HCV EIA is a qualitative test that detects human antibodies. This image shows several combinations of proteins used in different third-generation HCV EIA tests.

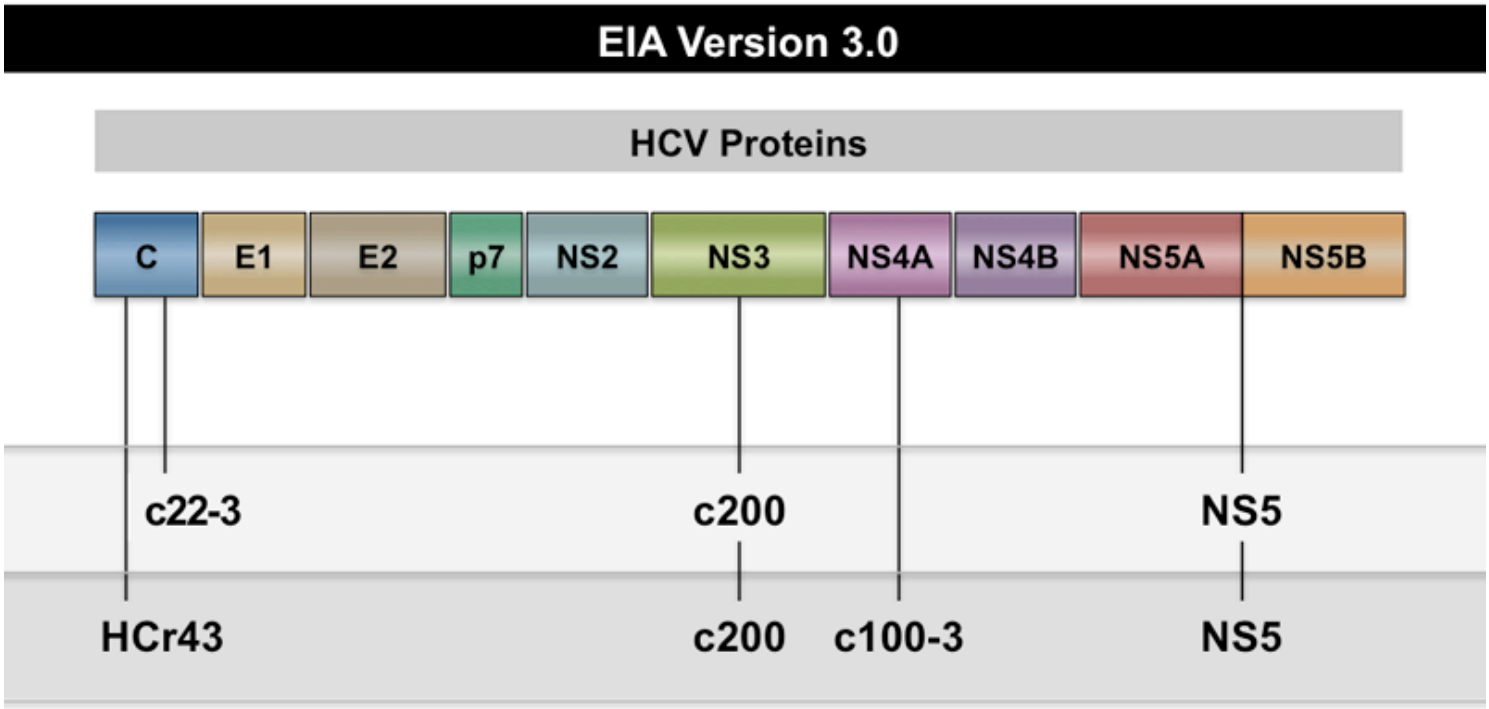

Figure 2 (Image Series) - OraQuick HCV Rapid Antibody Test (Image Series) - Figure 2 (Image Series) - OraQuick HCV Rapid Antibody Test
Image 2A: Test Kit Set-Up

This image shows the test device after it has been placed into the buffer in the developer solution vial. The test should be read 20 to 40 minutes after it is placed in the buffer.

Source: Image courtesy of OraSure Technologies, Inc.

Figure 2 (Image Series) - OraQuick HCV Rapid Antibody Test
Image 2B: Test Device

The OraQuick HCV Rapid Antibody Test can detect HCV antibodies in whole blood (obtained by fingerstick or venipuncture). The test device has control (C) and test (T) zones. If a line is visible only in the C zone (device on left), the test is considered nonreactive. If lines are visible in both the T and C zones (device on right), the test is considered reactive.

Source: Image courtesy of OraSure Technologies, Inc.

Figure 3 HCV Testing Sequence for Identifying Current HCV Infection

This diagram shows the HCV testing sequence recommended by the Centers for Disease Control and Prevention in May 2013.

Source: Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62:362-5.

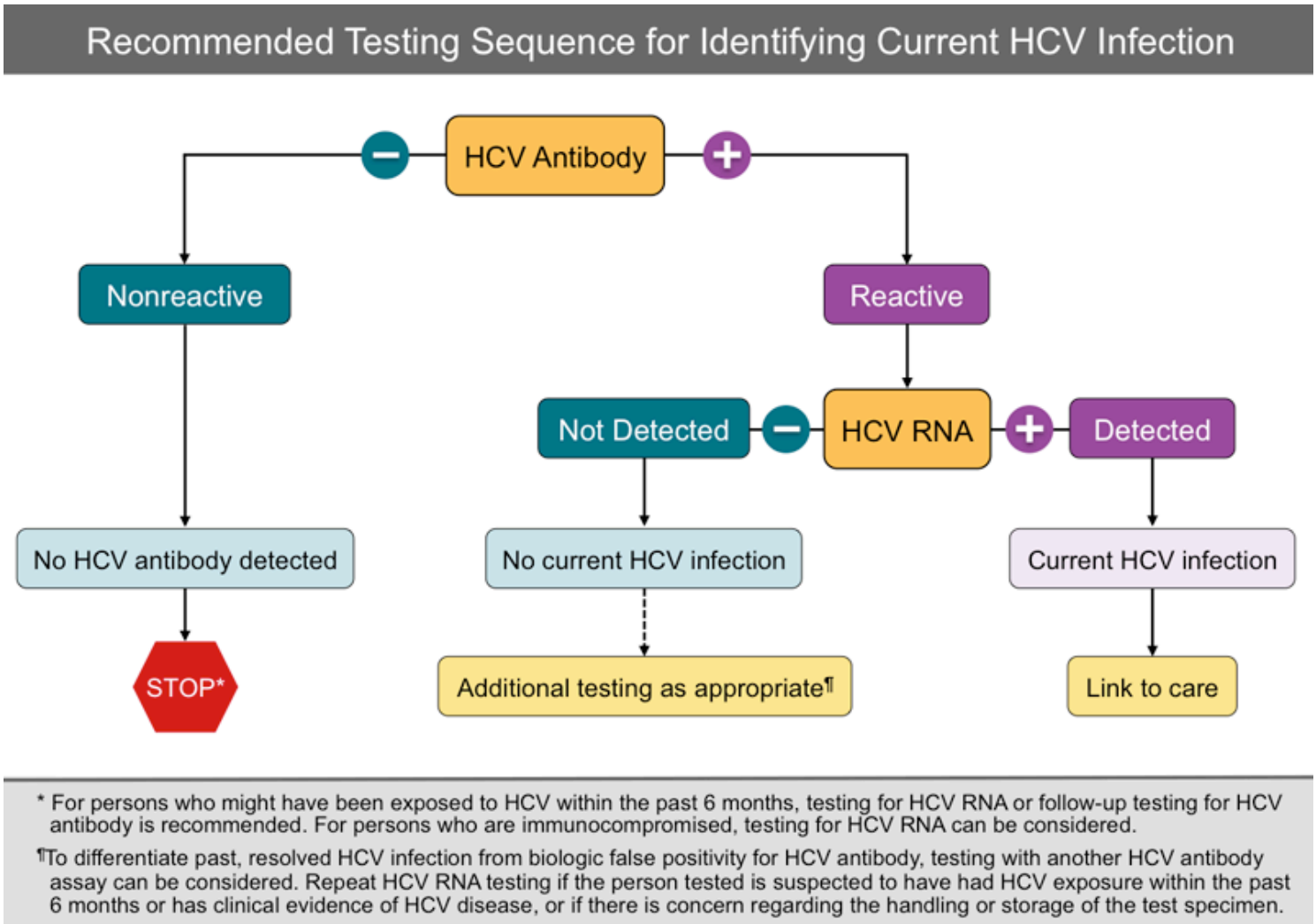

Figure 4 CDC Recommendations for Counseling for Persons with a Positive HCV RNA Test

The CDC recommends that persons newly diagnosed with HCV infection should receive some basic post-test counseling messages.

Source: Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep. 2012;61:1-32.

New Diagnosis of Hepatitis C Infection: Post-Test Counseling Messages

Persons infected with HCV can benefit from the following messages

- **Contact a health-care provider (either a primary-care clinician or specialist [e.g., in hepatology, gastroenterology, or infectious disease]), for**
  - medical evaluation of the presence or development of chronic liver disease;
  - advice on possible treatment options and strategies; and
  - advice on how to monitor liver health, even if treatment is not recommended.
- **Protect the liver from further harm by,**
  - considering hepatitis A and B vaccination if susceptible and if liver disease is present;
  - reducing or discontinuing alcohol consumption;
  - avoiding new medicines, including over-the-counter and herbal agents, without first checking with their health-care provider; and
  - obtaining HIV risk assessment and testing.
- **For persons who are overweight (BMI ≥25kg/m^2) or obese (BMI ≥30kg/m^2),**
  - consider weight management or losing weight and
  - follow a healthy diet and stay physically active.
- **To minimize the risk for transmission to others,**
  - do not donate blood, tissue, or semen and
  - do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers.

Figure 5 Interpretation of HCV Test Results and Recommended Action

Source: Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62:362-5.

Interpretation of Test Results for HCV Infection and Further Actions

Test Outcome	Interpretation	Further Action
HCV antibody nonreactive	No HCV antibody detected	• Sample can be reported as nonreactive for HCV antibody. No further action required. • If recent HCV 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 medical 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.

Table 1.

Interpretation of Hepatitis C Diagnostic Test Results

HCV Antibody	HCV RNA	Interpretation	Further Action / Counseling
Positive	Positive	• Current, active HCV infection	• Provide appropriate counseling regarding active HCV infection and link the individual to treatment
Positive	Negative	• Prior exposure to HCV; no current HCV infection. • Consistent with spontaneous clearance or prior HCV treatment.	• Individual remains susceptible to HCV. No linkage to care required.
Negative	Positive	• Acute HCV infection. • HCV likely acquired in the past 3 months.	• Provide appropriate counseling regarding active HCV infection and link individual to treatment.
Negative	Negatvie	• No HCV infection.	• Individual remain susceptible to HCV. No linkage to care required

Table 2.

Persons diagnosed with hepatitis C can benefit from the following messages:	
• **Contact a health-care provider (either a primary-care clinician or specialist [e.g., in hepatology, gastroenterology, or infectious disease]), for:** ◦ Medical evaluation of the presence or development of chronic liver disease; ◦ Advice on possible treatment options and strategies; and ◦ Advice on how to monitor liver health, even if treatment is not recommended.	
• **Protect the liver from further harm by:** ◦ Considering hepatitis A and B vaccination if susceptible and if liver disease is present; ◦ Reducing or discontinuing alcohol consumption; ◦ Avoiding new medicines, including over-the-counter and herbal agents, without first checking with their health-care provider; and ◦ Obtaining HIV risk assessment and testing.	
• **For persons who are overweight (BMI ≥25kg/m2) or obese (BMI ≥30kg/m^2):** ◦ Consider weight management or losing weight and ◦ Follow a healthy diet and stay physically active.	
• **To minimize the risk for transmission to others:** ◦ Do not donate blood, tissue, or semen and ◦ Do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers.	
Abbreviations: BMI = body mass index	

Source:

- Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep. 2012;61:1-32. [PubMed Abstract]