HEPATITIS C VIRUS (HCV) GENOTYPE TESTING

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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 Hepatitis C virus (HCV) genotype testing within 12 weeks prior to initiation of interferon-based treatment.

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

BACKGROUND

Currently, HCV genotype testing is used clinically to predict response to interferon-based therapy, to determine optimal treatment duration, to determine the appropriate dose of ribavirin, and to identify patients eligible for treatment with new direct acting antivirals. Since 2002, the standard of care (SOC) treatment for hepatitis C has been pegylated interferon and ribavirin. Nonetheless, interferon-based therapy has had limited success. It is estimated that 20-50% of patients treated with pegylated interferon and ribavirin will not achieve sustained
Virologic response. Viral genotype is the strongest predictor of response to interferon-based therapies, and current SOC treatment algorithms have been established based on specific viral genotypes.

There are at least six genotypes (genotypes 1-6) of HCV, and these differ by 30-35% in nucleotide sequence; these major genotypes can be further subdivided into subtypes (a,b,c,d...) that differ by up to 20-25%. The prevalence of viral genotypes varies with geography. Genotype 1 is prevalent in the US and Europe. Genotypes 3 and 4 are seen in Europe in the intravenous drug abuse population. Genotype 4 has frequently been isolated in North Africa. Genotype 2 is more prevalent in the Mediterranean region. Genotypes 5 and 6 are rare. Globally, most cases of HCV are genotype 1 infections, and in the US, 77% of cases are genotype 1 infections.

HCV genotype may play a role in the risk for disease progression. Recent studies suggest that patients with genotype 3 are at higher risk for a more rapid progression to liver fibrosis and have an increased risk for developing hepatocellular carcinoma.

New direct acting antiviral therapies have been introduced to improve response in patients with genotype 1. Boceprevir and telaprevir target a specific enzyme required for the virus life cycle. They are serine protease inhibitors that bind reversibly to the NS3 active site.

**CLINICAL EVIDENCE**

**HCV Treatment**

Cure rates with SOC, interferon-based therapy varies according to genotype, with genotypes 3, 5, and 6 achieving sustained virologic response (SVR) in over 80% of patients, and genotype 2 achieving SVR in about 80% of patients. Genotype 4 achieves SVR in slightly greater than 40% of cases. Genotype 1, the most prevalent genotype worldwide, has the lowest response rate to SOC therapy, at about 40%.

Studies of therapeutic responses in individuals infected with various genotypes have produced recommendations for pegylated interferon plus ribavirin treatment duration that are based on genotype. These studies look at response to therapy at certain critical treatment milestones in order to predict response. Patients with genotypes 2 and 3 require 24 weeks of SOC therapy to obtain sustained virologic response, whereas those individuals with genotypes 1 and 4 require 48 weeks of therapy. HCV genotyping and quantitative HCV RNA determinations provide prognostic information regarding likelihood of response, help optimize selection and dosing of treatment, provide information on optimal treatment duration, and help identify time points when therapy should be discontinued.

A recent meta-analysis of seven randomized, controlled trials concluded that patients with genotype 1 may have their SOC treatment course shortened to 24 weeks if they have a rapid virologic response characterized by undetectable HCV RNA at 4 weeks of therapy and if their baseline HCV viral load is low. An international panel has made a similar recommendation for shortening treatment course for patients with genotype 4 when a rapid virologic response is observed.
Ribavirin dosing is standardized to genotype. In a phase III, randomized, multicenter, double-blind clinical trial, it was established that patients with genotype 1 require weight-based dosing of ribavirin and that patients with genotype 2 and 3 can be treated with a lower dose over a shorter treatment course.

New direct acting antiviral drugs are specifically indicated for the treatment of HCV genotype 1 patients who tend to be more refractory to standard pegylated interferon plus ribavirin therapy. These agents, when combined with pegylated interferon and ribavirin, attain SVR rates ranging from 63 to 75% among treatment naive individuals. The treatment algorithm for each direct acting antiviral utilizes response guided therapy to determine the duration of treatment, often allowing for 24 rather than 48 weeks of therapy.

**Laboratory Testing**

HCV genotyping can be performed by two general methodologies: direct sequencing and reverse hybridization. Direct sequencing looks at the full sequence of a particular region of the HCV genome; reverse hybridization is restricted to the identification of specific nucleotides at limited positions, which are associated with a particular genotype or subtype. Line probe assays are a type of reverse hybridization that uses oligonucleotide probes. Of the commercially available HCV genotype tests, Trugene® 5’NC HCV Genotyping Kit (Siemens Medical Solutions Diagnostics) is a direct sequencing assay and VERSANT® HCV Genotype 2.0 Assay (Siemens Medical Solutions Diagnostics) is a line probe assay.

Commercial assays target the 5’ noncoding region (NCR) of the HCV genome because it is highly conserved. This target is useful for differentiating between genotypes; although it cannot reliably distinguish subtypes (e.g. 1a from 1b) and also may not reliably differentiate genotype 1 from the rarely occurring genotype 6. Newer versions of the commercially available assays target other regions of the genome to provide better characterization of genotype and subtype. For example, the Versant HCV Genotype 2.0 line assay (INNO-LiPA HCV 2.0), which targets the 5’NCR and core regions, shows improved characterization of genotype 6 compared to the earlier version of the assay. Abbott has introduced a real-time PCR based assay that targets both the 5’NCR and the NS5B gene. (NS5B is a viral protein required for replication.) A study comparing this assay to the Versant HCV Genotype 2.0 assay found good correlation between the assays.

Current methods cannot provide correct genotyping in a minority (3%) of cases. Mixed genotypes are uncommon and their clinical significance remains to be established.

Viral subtype data will likely need to be evaluated in order to study newer therapies that target specific HCV enzymes. It has been suggested that genotyping assays based only on the 5’ NCR should not be used for clinical trials requiring genotypic subtyping. The Abbott RealTime HCV Genotype II assay is reported to identify 93.2 % of subtype 1a and 88.9% of subtype 1b strains. The newer (2.0) version of the Versant assay has been reported to correctly subtype all genotype 3 subtypes, the majority of subtype 1 samples, but not subtypes for genotypes 2 and 4. The same study reports that a new HCV NS5b sequencing assay could subtype all samples not identified with 5’NCR assays. An NS5B microarray-based technique has been reported to have 100% genotyping concordance with gold standard phylogenetic analysis of the NS5B region and 99.7% concordance with the standard for subtyping.
Guidelines and Recommendations

Current clinical guidelines from societies regarding HCV genotype testing follow, and it should be noted that the most recent guidelines (published in 2011) were written after the phase III trials of boceprevir and telaprevir, two new direct acting antiviral drugs. The statement about standard of care therapy is in reference to interferon-based treatment.

American Association for the Study of Liver Diseases (AASLD)

The following recommendation derives from the American Association for the Study of Liver Diseases 2011 guidelines for treatment of genotype 1 HCV infections with new direct acting drugs:

- Patients with genotype 1 infections should be treated with a direct acting antiviral, boceprevir or telaprevir, plus peg interferon alfa and ribavirin.

This recommendation is from the American Association for the Study of Liver Disease, published in 2009:

- HCV genotype testing should be performed in all patients prior to treatment with interferon-based therapy to establish dose and length of treatment course and to predict probability of sustained virologic response.

American Association for the Study of Liver Diseases and Infectious Diseases Society of America

Recent 2014 guidelines from American Association for the Study of Liver Diseases and Infectious Diseases Society of America state that:

- 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.

European Association for the Study of the Liver (EASL)

The following recommendation derives from the most recent European Association for the Study of the Liver clinical practice guidelines, published in 2011:

- HCV viral genotype should be determined prior to antiviral therapy. For standard of care therapy, additional subtyping is not necessary.

The following recommendations are derived from the most recent European Association for the Study of the Liver (EASL) clinical practice guidelines on the Management of Hepatitis C Virus infection, published in 2014:

- 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.
- Combination of pegylated IFN-α and Ribavirin is the approved standard of care for chronic hepatitis C genotype 2, 3, 4, 5, and 6.
- IL28B genotyping is not a prerequisite for treating hepatitis C.
• During triple therapy in HCV genotype 1 patients, HCV RNA should be measured at weeks 4, 8, 12, 24, and at the end of treatment, when giving boceprevir. At weeks 4, 12, 24 and end of treatment, when giving telaprevir.
• During dual therapy, HCV RNA quantification should be measured at baseline, weeks 4, 12, 24 and end of treatment.
• At the end of treatment, virological response and SVR at week 12 or 24 must be assessed.
• Full adherence to all antiviral drugs should be the objective, in order to achieve optimum SVR and to reduce the risk of emergence of specific drug resistance.
• Obesity has an adverse effect on pegylated IFN-α and Ribavirin treatment. Weight control is recommended before initiating the treatment and may increase the likelihood of SVR.
• HCV genotype 1 infected patients who failed to eradicate HCV on prior treatment with dual therapy should be retreated with the triple combination.
• Patient with cirrhosis should undergo regular surveillance for HCC, irrespective of SVR.

US Preventive Services Task Force (USPSTF)

The following recommendations derived from the most recent publication by the US Preventive Services Task Force (USPSTF) on screening for and treatment of hepatitis C virus infection in asymptomatic adults.24

• 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.

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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REFERENCES


6. Hepatitis C virus. Figure 14. Laboratory Corporation of America Web site. https://www.labcorp.com/wps/portal/lut/p/c0/04_SB8K8xLMM9MSSzPy8x9s9C00s_hQV5NgQ09LYwP_kBB HA89A81BpC1NvY3dfQ_2CbEdFA05Gt_4I/?WCM_PORTLET=PC_7_UE451f9308G950IMN50RQC2054_WCM &WCM_GLOBAL_CONTEXT=/wps/wcm/connect/labcorp+content/LabCorp/Education+and+Research/Research/Virology/Hepatitis/Viruses/Hepatitis+C+Virus. (Accessed November 17, 2011.).


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| 10/23/2014 | Reference added in reference section: American Association For the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: http://www.hcvguidelines.org/ or https://www.med.upenn.edu/gastro/documents/HEPCguidelines.pdf (Accessed: October 21, 2014). Within the body of the policy, in the "BeaconLBS Recommendations" section, clarifying language was added. The recommendation itself has not changed. Within the body of the policy, in the "Guidelines and Recommendations" - "American Association for the Study of Liver Diseases (AASLD)" 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:  
• 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." |