Hepatitis C Virus Therapy Molecular Testing

Indications for Ordering

Predict response to therapy for chronic hepatitis C virus (HCV) infection

Tests to Consider

Recommended testing strategy

- Antibody or serology testing for screening
  - Preferred test is chemiluminescent immunoassay (CIA) with reflex to quantitative polymerase chain reaction (PCR)
- Quantitative RNA-PCR to confirm diagnosis and active infection
- Genotyping to guide choice of therapy
  - High-resolution genotyping by sequencing recommended when type/subtype determination is required (ie, non-6a/b vs type 1; type 1a vs 1b; presence of NS5 1B variants)
  - Low-resolution genotyping identifies general types without 1a, 1b subtyping

Screening test

Hepatitis C Virus Antibody by CIA with Reflex to HCV by Quantitative PCR 2010784

- Preferred reflex test for screening and confirmation of HCV in at-risk individuals
- If positive, testing will reflex to quantitative HCV PCR to confirm HCV infection

Hepatitis C Virus Antibody by CIA 2002483

- Preferred single screening antibody test for
  - One-time screening of population born between 1945 and 1965
  - Individuals at risk for HCV
- Positive results require confirmation by molecular testing

Recommended tests

Hepatitis C Virus (HCV) by Quantitative PCR with Reflex to HCV High-Resolution Genotype by Sequencing 2010793

- Preferred test to confirm active HCV infection following positive HCV screen when a higher level of subtype resolution is required

Hepatitis C Virus (HCV) by Quantitative PCR with Reflex to HCV Genotype by Sequencing 2002685

- Reflex test to confirm active HCV infection following positive HCV screen
- Reflex to genotype aids in prognosis and therapy selection

Hepatitis C Virus by Quantitative PCR 0098268

- Preferred single molecular test to confirm active HCV infection following positive HCV antibody screen
- Order only after positive HCV screen
- Use to monitor therapy

Hepatitis C Virus (HCV) Genotype with Reflex to HCV High-Resolution Genotype by Sequencing 2009255

- Reflex genotyping panel for prognosis and therapy selection when a higher level of subtype resolution is required
- Do not order prior to molecular confirmation of positive HCV screen
- Differentiates between type 1a and type 1b

Hepatitis C Virus High-Resolution Genotype by Sequencing 2006898

- Order before initiating HCV therapy to aid in prognosis and treatment selection when a higher level of subtype resolution is required (ie, non 6a/b vs type 1 and type 1a vs 1b)
- Do not order prior to molecular confirmation of positive HCV screen

Hepatitis C Virus Genotype by Sequencing 0055593

- Does not differentiate between type 1a and 1b, or between rare type 6 and type 1

Hepatitis C Virus (HCV) Genotype with Reflex to HCV NS5A Drug Resistance by Sequencing 2014598

- Order before initiating therapy with NS5A inhibitors
- Use to determine HCV type 1-6 after molecular confirmation of positive HCV screen
- If genotype “1a or 1b” is determined, testing will reflex to HCV NS5A for genotype differentiation and drug resistance by sequencing

Hepatitis C Virus NS5A Drug Resistance by Sequencing 2014139

- Order before initiating therapy with NS5A inhibitors
- Do not order prior to molecular confirmation of positive HCV screen and confirmation of genotype 1a or 1b

Hepatitis C Virus (HCV) NS3/4A Protease Inhibitor Resistance, GenoSure 2010647

- Recommended testing for HCV genotype 1 patients prior to initiating simprevir therapy
Disease Overview

Prevalence
Chronic HCV infection
- ~71 million cases worldwide (~1% of population) (WHO Global Hepatitis Report, 2017)
- ~2.7-3.9 million cases in U.S. (CDC)
- Most infected individuals remain undiagnosed

Therapy issues
- Acute HCV infection often leads to chronic disease
  - Therapy to treat disease depends on numerous clinical factors and HCV genotype
- At least 6 major HCV genotypes
  - HCV-1 accounts for 75% of U.S. cases
  - Genotyping helps to predict therapeutic response

Test Interpretation

Sensitivity/specificity
Analytical sensitivity/specificity – HCV quantitative PCR
- Detects all 6 major genotypes (1-6)
- No cross-reactivity observed with West Nile virus, influenza A, herpes simplex virus 1 or 2, human cytomegalovirus, adenovirus type 2, probionibacterium acnes, Candida albicans, Staphylococcus aureus, human T-lymphocyte virus types I and II, Epstein-Barr virus, human herpesvirus type 6, St. Louis encephalitis virus, Dengue virus types 1-4, yellow fever virus, Zika virus, Banzi virus, Ilheus virus, FSME virus, hepatitis G virus, hepatitis A virus, HIV-1, or hepatitis B virus
- Limit of detection, all genotypes – 15 IU/mL (1.2 log IU/mL)
- Limit of quantification, all genotypes – 15-100,000,000 IU/mL (1.2-8.0 log IU/mL)
- Conversion factor – 2.7 copies/IU

Limitations
- Serologic testing cannot be used to confirm active infection
  - Positive serology results can indicate a false-positive result or recovery following exposure
- The low-resolution genotyping test
  - Does not distinguish between subtypes 1a and 1b
  - Does not discriminate rare type 6 virus from type 1

References