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 nucleic acid amplification testing (NAAT)
- Quantitative NAAT to confirm diagnosis and active infection
- Genotyping to guide therapy decisions
  - 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 tests

Hepatitis C Virus Antibody by CIA with Reflex to HCV by Quantitative NAAT 2010784
- Preferred reflex test for screening and confirmation of HCV in at-risk individuals
- If positive, testing reflexes to quantitative HCV NAAT 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 NAAT with Reflex to HCV High-Resolution Genotype by Sequencing 3000577
- Confirm active HCV infection following positive HCV screen when a higher level of subtype resolution is required

Hepatitis C Virus (HCV) by Quantitative NAAT with Reflex to HCV Genotype by Sequencing 3000576
- Reflex test to confirm active HCV infection following positive HCV screen
- Reflex to genotype aids in prognosis and therapy selection

Hepatitis C Virus (HCV) by Quantitative NAAT 3000572
- 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 (HCV) 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 simeprevir 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 six 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 NAAT
- Detects all 6 major genotypes (1-6)
- No cross-reactivity observed with hepatitis A virus, hepatitis B virus, hepatitis G virus, HIV-1, HIV-2, herpes simplex virus (HSV-1, HSV-2), human herpes virus 6B, human herpes virus 8, human T-cell lymphotropic virus (HTLV-1, HTLV-2), parvovirus B19, West Nile virus, Dengue virus (types 1-4), cytomegalovirus, Epstein-Barr virus, rubella virus, human papillomavirus, adenovirus type 5, influenza A virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, Yellow fever virus, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, Candida albicans, Staphylococcus epidermidis, Propionibacterium acnes, Staphylococcus aureus, Streptococcus pneumonia, Corynebacterium diphtheriae
- Limit of detection, all genotypes – 5.2 IU/mL (0.7 log IU/mL)
- Limit of quantification, all genotypes – 10-100,000,000 IU/mL (1.0-8.0 log IU/mL)

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