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

- Preferred reflex test to confirm active HCV infection following positive HCV screen
- 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
- Do not order prior to molecular confirmation of positive HCV screen

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) GenoSure NS3 and NS4A 3001234

- Recommended testing for HCV genotype 1 patients prior to initiating simeprevir therapy. Identifies the Q80K polymorphism.

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 six 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*, *Cornybacterium 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
- Low-resolution genotyping test
  - Does not distinguish between subtypes 1a and 1b
  - Does not discriminate rare type 6 virus from type 1

References

- Centers for Disease Control and Prevention (CDC). Hepatitis C FAQs for health professionals. https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1 [Updated: Feb 2018; Accessed: Apr 2018]
- World Health Organization (WHO). Global Hepatitis Report, 2017. http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ [Published: Apr 2017; Accessed: Oct 2017]