

Hepatitis C Viral RNA Genotype 1 NS5A Drug Resistance

Test Code: 906678

Specimen Requirements: 2 mL frozen plasma from an EDTA lavender-top tube (0.6 mL minimum).

CPT Code*: 87902

CLINICAL USE

- Identify *NS5A* polymorphisms associated with resistance to *NS5A* inhibitor therapy in patients with hepatitis C virus (HCV) genotype 1
- Identify resistance-associated mutations as potential cause of *NS5A* inhibitor failure
- Guide selection of antiviral therapy in patients with hepatitis C virus (HCV) genotype 1

CLINICAL BACKGROUND

HCV infection affects more than 3.5 million individuals in the United States.¹ Left untreated, it can lead to progressive liver injury, cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. Of the 6 major HCV genotypes, genotype 1 (including subtypes 1a and 1b) is the most prevalent by far in the United States.² Combination therapy with pegylated interferon (PEG) plus ribavirin was the mainstay of treatment for all genotypes, but resulted in low sustained virologic response rates of approximately 40% to 50% in HCV genotype 1-infected patients.^{3,4} In addition, severe adverse effects remain a limitation of PEG-based therapy.

The availability of direct-acting antivirals (DAAs) has led to PEG-free treatment options for all HCV genotypes.⁵ DAAs interrupt HCV replication by targeting specific HCV proteins, such as the *NS5A* protein, *NS5B* polymerase, and *NS3/4A* protease.⁶ DAAs that inhibit *NS3/4A* (simeprevir, paritaprevir, grazoprevir), *NS5A* (daclatasvir, ledipasvir, ombitasvir, elbasvir), and *NS5B* (sofosbuvir, dasabuvir) have been approved for treatment of HCV infection and are available in fixed-dose combinations.⁷⁻⁹ Additional DAAs in development may expand such options.¹⁰

The high mutation rate of the HCV genome, combined with selective pressure from ongoing therapy, can lead to

selection of HCV variants that are resistant to DAAs.^{11,12}

Resistance-associated substitutions in the *NS5A* gene have been detected following treatment of genotype 1a or 1b HCV infection with *NS5A* inhibitors.¹² The AASLD/IDSA HCV Guidance Panel recommends testing for these substitutions when *NS5A* inhibitors fail.⁵ Baseline *NS5A* polymorphisms may also impact the emergence of *NS5A* resistance.¹³ Testing for the presence of *NS5A* polymorphisms is recommended at baseline for patients with HCV genotype 1a prior to initiation of treatment with elbasvir plus grazoprevir⁹ and should also be considered for patients with genotype 1a and cirrhosis prior to sofosbuvir plus daclatasvir treatment.¹⁴

The Hepatitis C Viral RNA Genotype 1 *NS5A* Drug Resistance assay determines the HCV genotype (1a, 1b or 1) and detects mutations associated with resistance to *NS5A* inhibitors. The principal HCV *NS5A* mutations associated with resistance to the *NS5A* inhibitors include those identified at codons 28, 30, 31, 58, and 93.⁶ The identification of specific mutations or polymorphisms may be useful to optimize treatment selection.

INDIVIDUALS SUITABLE FOR TESTING

- Individuals with genotype 1 HCV infection who experience treatment failure with an *NS5A* inhibitor
- Individuals with genotype 1 HCV infection who are being considered for an *NS5A* inhibitor

METHOD

- Reverse transcription polymerase chain reaction (PCR) and DNA sequencing of *NS5A* codons 1 to 150
- Analytical sensitivity: >95% for viral loads $\geq 1,800$ IU/mL
- Results reported
 - HCV genotype: 1a, 1b, 1, or not detected (genotypes other than 1 may not be detected)
 - Daclatasvir resistance: probable or not predicted
 - Ledipasvir resistance: probable or not predicted
 - Ombitasvir resistance: probable or not predicted
 - Elbasvir resistance: probable or not predicted

INTERPRETIVE INFORMATION

An interpretation of “resistance probable” suggests that the patient’s viral population may show reduced susceptibility to *NS5A* inhibitor-containing regimens and that treatment

failure may be due to the presence of an *NS5A* mutation. Consult the package inserts of the applicable *NS5A* inhibitor-containing products for treatment guidelines if *NS5A* polymorphisms are reported. An interpretation of “resistance not predicted” suggests that resistance to *NS5A* inhibitors is unlikely.

Resistance may also be affected by as yet uncharacterized mutations and interactions among mutations. Failure to obtain a genotype may be due to insufficient virus, a non-1 genotype, mutations in the viral genome at the assay priming sites, or the presence of an inhibitory substance in the sample.

References

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* The CPT code provided is based on AMA guidelines and is for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

This test was developed and its performance characteristics have been determined by Focus Diagnostics. Performance characteristics refer to the analytical performance of the test.