

# Hepatitis C Viral RNA Genotype 3 NS5A Drug Resistance

**Test Code:** 906677

**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 3
- Identify resistance-associated mutations as potential cause of daclatasvir failure
- Guide selection of antiviral therapy in patients with hepatitis C virus (HCV) genotype 3

## CLINICAL BACKGROUND

HCV infection affects more than 3.5 million individuals in the United States.<sup>1</sup> Left untreated, it can lead to progressive liver injury, cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. Genotype 3, one of 6 major HCV genotypes, constitutes 10% of HCV infections in the United States and Canada.<sup>2</sup> Patients with this HCV genotype have a higher incidence of hepatocellular carcinoma, higher prevalence of steatosis and insulin resistance, and faster rates of fibrosis progression compared to patients with other HCV genotypes.<sup>3</sup> Combination therapy with pegylated interferon (PEG) plus ribavirin was the mainstay of treatment for all genotypes and resulted in sustained virologic response rates of 70% to 80% in HCV genotype 3-infected patients.<sup>3</sup> Severe adverse effects remain a limitation of PEG-based therapy, however.

The availability of direct-acting antivirals (DAAs) has led to PEG-free treatment options for all HCV genotypes.<sup>4</sup> DAAs interrupt HCV replication by targeting specific HCV proteins, such as the *NS5A* protein, *NS5B* polymerase, and *NS3/4A* protease.<sup>5</sup> DAAs that are recommended for the treatment of genotype 3-infected HCV patients include the *NS5B* inhibitor sofosbuvir and the *NS5A* inhibitor daclatasvir.<sup>4,6</sup> Additional DAAs in development may expand such options.<sup>7</sup>

In clinical studies, the baseline *NS5A* polymorphism Y93H resulted in the reduced rates of sustained virologic response in patients with HCV genotype 3 who were treated for 12 weeks with daclatasvir plus sofosbuvir, especially in those patients with cirrhosis.<sup>6,8</sup> In addition, the high mutation rate of the HCV genome, combined with selective pressure from ongoing therapy, can lead to selection of additional HCV variants that are resistant to *NS5A* inhibitors.<sup>9,10</sup>

The Hepatitis C Viral RNA Genotype 3 *NS5A* Drug Resistance test determines the HCV genotype (3a or 3) and detects mutations, including the Y93H polymorphism, associated with resistance to the *NS5A* inhibitor daclatasvir.<sup>8</sup> The identification of specific mutations or polymorphisms may be useful to optimize treatment selection.

## INDIVIDUALS SUITABLE FOR TESTING

- Individuals with genotype 3 HCV infection who experience treatment failure with a daclatasvir-containing regimen
- Individuals with genotype 3 HCV infection who are being considered for a daclatasvir-containing regimen

## METHOD

- Reverse transcription polymerase chain reaction (PCR) and DNA sequencing of genotype *NS5A* codons 1 to 150
- Analytical sensitivity: >95% for viral loads  $\geq 1,300$  IU/mL
- Results reported
  - HCV genotype: 3a, 3, or not detected (genotypes other than 3 may not be detected)
  - Daclatasvir resistance: predicted or not predicted

## INTERPRETIVE INFORMATION

An interpretation of “resistance predicted” suggests that the patient’s viral population may show reduced susceptibility to daclatasvir and that treatment failure may be due to the presence of an *NS5A* mutation. An interpretation of “resistance not predicted” suggests that resistance to daclatasvir 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-3 genotype, mutations in the viral genome at the assay priming

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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.