CMV Resistance: Letermovir
Test Code: 30722

Clinical and Procedure

Clinical Utility
Human Cytomegalovirus (CMV) infections are a major cause of morbidity and mortality among immunocompromised patients. Letermovir targets subunit 2 of the viral terminase complex (UL56) and is approved for CMV prophylaxis in adult hematopoietic stem cell transplant (HSCT) recipients. Proper patient management requires rapid detection of resistance. Laboratory testing should be used to confirm the occurrence of drug resistance, as treatment modification based solely on clinical suspicion may result in added toxicity and increased complexity in patient management. The CMV Resistance: Letermovir sequencing assay is designed to detect identified mutations in the UL56 genes of CMV. The use of genotypic sequencing offers a rapid turnaround time, a broad range of antiviral resistance information, and the ability to provide information concerning new drugs as they become available.

<table>
<thead>
<tr>
<th>Assay</th>
<th>UL</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>NEW</em> CMV Resistance: Letermovir, Ganciclovir, Foscarnet, Cidofovir</td>
<td>54, 56, and 97</td>
<td>Terminase, Polymerase and Phosphotransferase</td>
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<tr>
<td>CMV Resistance: Ganciclovir, Foscarnet, Cidofovir (formerly known as: CMV Antiviral Resistance Sequencing or CMV AVR)</td>
<td>54 and 97</td>
<td>Polymerase and Phosphotransferase</td>
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<tr>
<td><em>NEW</em> CMV Resistance: Letermovir</td>
<td>56 only</td>
<td>Terminase</td>
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About CMV Resistance Testing
Cytomegalovirus, also known as human herpesvirus 5, is a highly ubiquitous, double-stranded DNA virus in the Betaherpesvirinae subfamily. Serological studies have demonstrated that a majority of adults in the United States have been infected with CMV. Following primary infection, CMV establishes a lifelong latent infection, which may reactivate in both immunocompetent and immunocompromised individuals. In immunocompromised patients, primary or reactivated CMV infections can cause a range of symptoms like fever and fatigue and diseases that may include interstitial pneumonia, gastrointestinal infection, central nervous system disease, hepatitis, retinitis, and encephalitis. CMV reactivations have also been reported to occur frequently in critically ill immunocompetent patients and are associated with prolonged hospitalization or death. Due to the severity of these conditions and even life threatening outcomes, treatment of CMV diseases with antiviral drugs is common. Additionally, prophylactic treatment with antiviral drugs is used to prevent the occurrence of disease in high-risk patients. Anti-CMV drugs currently available for either treatment or prophylaxis include ganciclovir, valganciclovir (the orally administered prodrug), foscarnet, cidofovir, and letermovir. Ganciclovir targets both UL97 and UL54, while cidofovir and foscarnet target only UL54. The newest CMV drug, Letermovir, targets subunit 2 of the viral terminase complex (UL56). Viral UL97 phosphotransferase gene, and UL54 polymerase genotypic mutations are well documented mechanisms of resistance to these antiviral drugs. Mutations within UL56 have been shown to confer resistance to Letermovir. Drug resistance should be suspected if quantitative CMV PCR viral load values either persist or increase, or if CMV disease presents, after several weeks of treatment with an appropriate dose.

Procedure
Conventional PCR followed by genotypic sequencing. Sequencing analysis provides information on selected locations in one gene involved in CMV antiviral resistance for Letermovir: UL56. This test has not been cleared or approved for diagnostic use by the U.S. Food and Drug Administration.

Specificity
CMV sequencing analysis provides information about selected locations in the UL56 gene involved in CMV antiviral resistance.

Turnaround Time
2-4 business days from receipt of specimen.
Specimen Information

<table>
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<tr>
<th>Specimen Type</th>
<th>Order Code</th>
<th>CPT Code</th>
<th>NY Approved</th>
<th>Volume</th>
<th>Assay Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>30722</td>
<td>87910</td>
<td>Yes</td>
<td>2 mL (min. 100 IU/mL)</td>
<td>Mutations in the UL56 gene will be reported as Resistant/None Detected. Interpretation of gene mutations and association with antiviral resistance to letermovir will be provided with the report. See CMV Resistance Mutations for more information.</td>
</tr>
</tbody>
</table>

Special Instructions
- Collect 4-5 mL whole blood in EDTA, ACD or PPT.
- Centrifuge and transfer 2 mL plasma to a sterile, screw top tube.
- Can be shipped at ambient or frozen temperature Monday through Friday.
- Specimens shipped at ambient temperature must be received within 7 days of collection.
- Stability: 7 days ambient, 7 days refrigerated, 60 days frozen.

Shipping
Ship Monday through Friday. Friday shipments must be labeled for Saturday delivery. All specimens must be labeled with patient's name and collection date. A Viracor Eurofins test requisition form must accompany each specimen. Multiple tests can be run on one specimen. Ship specimens FedEx Priority Overnight® to: Viracor Eurofins, 1001 NW Technology Dr, Lee's Summit, MO 64086.

Causes for Rejection
CMV DNA concentrations too low to allow antiviral resistance testing (see above for minimum volume and viral load), whole blood frozen, specimens beyond their acceptable length of time from collection as listed in the specimen handling, or specimen types other than those listed.

Disclaimer
Specimens are approved for testing in New York only when indicated in the Specimen Information field above. The CPT codes provided are based on Viracor Eurofins' interpretation of the American Medical Association's Current Procedural Terminology (CPT) codes and are provided for informational purposes only. CPT coding is the sole responsibility of the billing party. Questions regarding coding should be addressed to your local Medicare carrier. Viracor Eurofins assumes no responsibility for billing errors due to reliance on the CPT codes illustrated in this material.

References