

Cytomegalovirus Drug Resistance by Next Generation Sequencing, Ganciclovir, Foscarnet, Cidofovir, Maribavir, and Letemovir

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Cytomegalovirus (CMV) is a common infection among both children and adults that is generally asymptomatic in infected immunocompetent children and adults, but can lead to serious complications in neonates, pregnant individuals, immunocompromised individuals, and transplant recipients.¹ Next generation sequencing can be used to test for CMV antiviral resistance with greater sensitivity to detect resistant subpopulations than traditional Sanger sequencing.² This test sequences resistance-associated mutations in the *UL27*, *UL54*, *UL56*, and *UL97* genes to assess resistance to ganciclovir, foscarnet, cidofovir, maribavir, and letemovir.

Featured ARUP Testing

[Cytomegalovirus Drug Resistance by Next Generation Sequencing, Ganciclovir, Foscarnet, Cidofovir, Maribavir, and Letemovir 3004615](#)

Method: Massively Parallel Sequencing

Provides antiviral susceptibility information for ganciclovir, foscarnet, cidofovir, maribavir, and letemovir. Intended for patients with viral load >2.6 log IU/mL.

The reference sequence for CMV antiviral resistance testing is Merlin strain genbank ID NC_006273.

Test Interpretation

Limitations

- Specimens with viral loads <2.6 log IU/mL may fail to amplify, thus producing indeterminate results.
- This test detects populations down to 10% of the total population, which may account for resistance interpretation differences between methods.

Evaluated Mutations

UL27 Variants						
Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letemovir	Confirmed by Phenotyping
A269T ³	–	–	–	P	–	Y
A406V ^{3,4}	–	–	–	P	–	Y
C415* ^{3,4}	–	–	–	P	–	Y
D534Y ⁵	–	–	–	P	–	Y
E22* ³	–	–	–	P	–	Y
K89N ⁶	–	–	–	S	–	Y
L193F ³	–	–	–	P	–	Y
L335P ^{3,7}	–	–	–	R	–	Y
L426F ³	–	–	–	P	–	Y
R233S ^{4,5}	–	–	–	P	–	Y
R448P ⁵	–	–	–	P	–	Y
V353E ³	–	–	–	P	–	Y
W153R ³	–	–	–	P	–	Y
W362* ³	–	–	–	P	–	Y

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
W362R ⁴	–	–	–	P	–	Y
<i>UL54 Variants</i>						
Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
883-884ins ⁸	–	–	–	–	–	N
981-982del ^{9,10,11,12,13,14,15,16,17,18,19}	R	R	R	–	–	Y
A505V ^{8,15}	P	S	P	–	–	Y
A543P ^{16,20}	R	S	R	–	–	Y
A809V ^{10,11,12,15,19,21,22,23,24,25}	P	R	R	–	–	Y
A834P ^{14,15,26}	R	R	R	–	–	Y
A987G ^{10,15,19,27,28,29,30}	R	S	R	–	–	Y
A987V ^{18,19}	S	R	S	–	–	Y
C524del ^{15,31}	R	S	R	–	–	Y
C539G ^{15,32}	R	S	R	–	–	Y
C539R ^{33,34}	R	S	R	–	–	Y
C590F ³⁵	S	R	S	–	–	Y
D301N ^{11,12,15,19}	R	S	R	–	–	Y
D413A ^{14,15,36}	R	S	R	–	–	Y
D413E ^{10,11,12,14,15,28,37,38}	R	S	R	–	–	Y
D413N ^{15,32}	R	S	R	–	–	Y
D413Y ^{15,39}	R	S	R	–	–	Y
D515E ^{10,40,41}	P	P	R	–	–	Y
D515G ¹¹	S	S	S	–	–	Y
D515Y ^{15,16,17,19,41}	P	P	R	–	–	Y
D542E ^{15,42}	R	S	S	–	–	Y
D588E ^{10,28,30}	S	R	S	–	–	Y
D588N ^{12,15,23,28,43}	P	R	R	–	–	Y
D594N ¹⁸	S	S	S	–	–	Y
E303D ^{15,39}	R	S	R	–	–	Y
E303G ^{15,39}	R	S	R	–	–	Y
E756D ^{11,12,15}	S	R	S	–	–	Y
E756G ⁴⁴	S	R	S	–	–	Y
E756K ^{11,12,15,23,28,45,46,47,48}	P	R	R	–	S	Y
E756Q ^{12,15,21,49}	S	R	S	–	–	Y
E951D ^{15,24}	S	R	R	–	–	Y
E989D ¹⁸	P	R	R	–	–	Y
F412C ^{10,12,15,19,30,50}	R	S	R	–	–	Y

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letemovir	Confirmed by Phenotyping
F412L ^{15,19,23}	R	S	R	—	—	Y
F412S ^{15,23,34,51}	R	S	R	—	—	Y
F412V ^{10,15,28,30}	R	S	R	—	—	Y
F595J ^{15,33,34}	S	R	S	—	—	Y
G841A ^{14,15,22}	R	R	R	—	—	Y
G841S ⁸	S	P	P	—	—	Y
G971D ¹¹	S	S	S	—	—	Y
H600L ⁴⁴	R	R	R	—	—	Y
I521T ^{15,40,52}	R	S	R	—	—	Y
I722V ¹⁰	R	S	R	—	—	N
I726T ^{8,15}	P	S	P	—	—	Y
I726V ^{8,15}	R	S	R	—	—	Y
K493N ¹⁸	R	R	R	—	—	Y
K500N ^{15,33,34}	R	S	R	—	—	Y
K513E ^{10,12,15,28,30}	R	S	R	—	—	Y
K513N ^{10,12,15,28,37,53,54}	R	S	R	—	—	Y
K513Q ³⁵	R	S	R	—	—	Y
K513R ^{10,15,19,32}	R	S	R	—	—	Y
K513T ¹⁸	R	S	R	—	—	Y
K805Q ^{10,15,21,22,30}	R	S	S	—	—	Y
L501F ^{10,28,35,37,51,55}	R	S	R	—	—	Y
L501I ^{10,12,15,28,30,56}	R	S	R	—	—	Y
L516M ⁵⁷	S	S	S	—	—	Y
L516P ^{17,19}	R	S	R	—	—	Y
L516R ^{11,12,15}	R	S	R	—	—	Y
L516W ^{15,58}	R	S	R	—	—	Y
L545F ³⁵	R	S	R	—	—	Y
L545S ^{10,12,15,30,33,59}	R	S	R	—	—	Y
L545W ^{15,19,23,34}	R	S	R	—	—	Y
L565V ¹⁸	P	R	P	—	—	Y
L773V ^{15,32,60}	R	R	R	—	—	Y
L776M ^{14,15,61}	S	R	R	—	—	Y
L802M ^{12,14,15,21,28,30,33,43,50,59}	S	R	P	—	—	Y
L802V ³³	S	S	P	—	—	Y
L862F ³³	S	S	P	—	—	Y
L897P ⁶²	—	—	S	—	—	Y

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letemovir	Confirmed by Phenotyping
L957F ^{15,33,34}	S	S	R	—	—	Y
M393K ^{10,63}	R	R	R	—	—	N
M393R ^{10,63}	R	R	R	—	—	N
M844T ^{15,64}	S	R	S	—	—	Y
M844V ^{15,64}	S	R	R	—	—	Y
N408D ^{10,12,15,19,28,30,33,59,65}	R	S	R	—	—	Y
N408H ³⁵	R	S	R	—	—	Y
N408K ^{15,19,23,26,39}	R	S	R	—	—	Y
N408S ^{15,31,66}	R	S	R	—	—	Y
N410K ^{11,15,19}	R	S	R	—	—	Y
N495K ^{14,15,24,67}	S	R	S	—	—	Y
P488R ^{32,33}	R	S	R	—	—	Y
P497S ¹⁸	R	S	P	—	—	Y
P522A ^{10,15,52}	R	S	R	—	—	Y
P522S ^{10,15,19,23,30,52}	R	S	R	—	—	Y
P522T ³⁵	R	S	R	—	—	Y
P829S ^{15,33,34}	S	S	R	—	—	Y
Q578H ^{15,19,23,34,60}	R	R	R	—	—	Y
Q578L ^{8,15}	S	P	P	—	—	Y
Q783R ²⁴	S	P	P	—	—	Y
Q807A ²¹	—	R	—	—	—	Y
R1052C ⁶⁸	S	S	S	—	—	Y
S290R ^{15,24}	S	R	P	—	—	Y
S585A ^{15,33,34}	S	R	S	—	—	Y
T419M ⁶⁰	—	R	S	—	—	N
T503A ³⁵	R	S	R	—	—	Y
T503I ^{10,11,12,14,15}	R	S	R	—	—	Y
T552N ^{15,24,33,34}	S	R	R	—	—	Y
T700A ^{10,12,15,19,21,25,30,69}	P	R	S	—	—	Y
T813S ^{14,15,22}	R	R	R	—	—	Y
T821I ^{10,12,14,15,21,30}	S	R	R	—	—	Y
T838A ^{14,15,43}	S	R	S	—	—	Y
V526L ^{15,46}	R	S	R	—	—	Y
V715A ^{15,58}	S	R	S	—	—	Y
V715M ^{10,12,15,21,25,30,49,69}	S	R	S	—	—	Y
V781I ^{15,23,28,30}	S	R	P	—	—	Y

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
V787A ^{15,41,48}	S	R	R	—	—	Y
V787E ^{20,48}	R	R	R	—	—	Y
V787I ¹²	—	R	—	—	—	N
V787L ^{14,15,21,33,49,70}	S	R	R	—	—	Y
V812L ^{10,12,14,15,21,33,39,43,54}	R	R	R	—	—	Y
V823A ¹⁸	R	S	R	—	—	Y
V946L ^{15,33,34}	S	R	S	—	—	Y
Y751H ¹⁰	R	S	R	—	—	N

UL56 Variants

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
A365S ^{16,20}	—	—	—	—	R	Y
C25F ¹⁶	—	—	—	—	R	Y
C325F ^{71,72}	—	—	—	—	R	Y
C325R ^{71,72}	—	—	—	—	R	Y
C325W ^{16,72}	—	—	—	—	R	Y
C325Y ^{16,71,72,73}	—	—	—	—	R	Y
E237D ^{71,72,74}	—	—	—	—	R	Y
E237G ^{72,75}	S	S	—	—	R	Y
F261C ^{71,72}	—	—	—	—	R	Y
F261L ^{71,72,74}	—	—	—	—	R	Y
F261S ⁷²	—	—	—	—	R	N
K258E ⁷⁴	—	—	—	—	R	Y
L241P ^{71,73,76,77}	—	—	—	—	R	Y
L254F ^{20,77}	—	—	—	—	R	Y
L257F ^{16,20,77}	—	—	—	—	R	Y
L257I ^{71,72}	—	—	—	—	R	Y
L328V ^{16,20}	—	—	—	—	R	Y
M329T ^{71,72,74}	—	—	—	—	R	Y
N232Y ⁷⁴	—	—	—	—	R	Y
N368D ^{20,77}	—	—	—	—	R	Y
Q204R ⁷⁴	—	—	—	—	P	Y
R369G ^{72,73}	—	—	—	—	R	Y
R369M ^{72,73,77}	—	—	—	—	R	Y
R369S ^{72,73,76}	—	—	—	—	R	Y
R369T ^{20,74}	S	S	S	—	R	Y
S229F ^{20,77}	—	—	—	—	R	Y

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
T244K ^{71,72}	–	–	–	–	R	Y
T244R ⁷²	–	–	–	–	R	N
V231A ^{71,72}	–	–	–	–	R	Y
V231L ^{16,71,72,73,77}	–	–	–	–	R	Y
V236A ^{16,20}	–	–	–	–	R	Y
V236L ^{71,72}	–	–	–	–	R	Y
V236M ^{16,47,72,73,77,78}	S	S	S	–	R	Y
Y321C ^{71,72}	–	–	–	–	R	Y

UL97 Variants

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
590-593del ^{10,59}	S	S	R	–	–	Y
590-600del ^{10,79}	–	–	R	–	–	N
590-603del ^{10,37}	–	–	R	–	–	N
590-607del ¹⁵	–	–	R	–	–	N
591-594del ^{10,12,80,81}	–	–	R	–	–	Y
591-607del ^{10,82}	–	–	R	–	–	Y
595-603del ^{10,12,70,81,83}	–	S	R	–	–	Y
597-598del ^{15,81}	–	–	R	–	–	Y
597-599del ^{58,81}	–	–	R	–	–	Y
597-603del ⁵¹	–	–	–	–	–	N
600-601del ^{10,15,70,81}	–	–	R	–	–	Y
601-602del ^{15,81}	–	–	R	–	–	Y
601-603del ^{36,81}	S	S	R	–	–	Y
A590T ^{10,80,84}	–	–	R	–	–	N
A591D ^{10,80,84}	–	–	R	–	–	N
A591V ^{15,16,81}	–	–	R	–	–	Y
A594E ^{14,15,85}	–	–	R	–	–	Y
A594G ^{15,66,86}	–	–	R	–	–	Y
A594P ^{10,35,51,87,88}	–	–	R	–	–	Y
A594S ^{20,89}	–	–	R	–	–	Y
A594T ^{12,15,45,58,80,82,90,91}	–	–	R	–	–	Y
A594V ^{12,13,15,51,69,79,80,81,87,90,92}	–	–	R	–	–	Y
A606D ^{10,80,84}	–	–	P	–	–	N
A613V ^{15,57,66}	–	–	R	–	–	Y
A619V ^{15,58}	–	–	S	–	–	Y
A674T ^{15,93}	–	–	S	–	–	Y

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
C480F ^{18,20}	—	—	R	R	—	Y
C480R ^{15,94}	—	—	R	R	—	Y
C518Y ^{15,66,95}	—	—	R	—	—	Y
C592F ¹⁰	—	—	R	—	—	N
C592G ^{12,13,15,18,24,28,80,81,82,87,92}	S	S	R	—	—	Y
C603R ^{14,15,92,96}	—	—	R	—	—	Y
C603S ^{14,15,85,92}	—	—	P	—	—	Y
C603W ^{10,12,15,51,53,80,87,92}	S	S	R	—	—	Y
C603Y ^{10,80,84}	—	—	R	—	—	N
C607F ^{10,15,82,90}	—	—	R	—	—	Y
C607Y ^{9,12,15,51,80,82,97,98}	—	S	R	—	—	Y
D456N ^{20,94}	—	—	R	R	—	Y
D605E ^{13,15,20}	—	—	S	—	—	Y
E362D ⁹⁹	—	—	R	S	—	Y
E596D ^{15,40}	—	—	S	—	—	Y
E596G ^{10,12,15,45,53,80,82}	—	—	R	—	—	Y
E596Q ³⁵	—	—	R	—	—	Y
E596Y ^{15,40}	—	—	R	—	—	Y
E596del ^{15,81}	—	—	R	—	—	Y
E655K ^{15,46}	—	—	S	—	—	Y
F342S ^{15,100,101,102}	—	—	R	R	—	Y
F342Y ^{20,103}	—	—	R	R	—	Y
G598S ^{10,12,104}	—	—	R	—	—	Y
G598V ^{10,84}	—	—	R	—	—	N
H411L ^{5,20,105}	—	—	—	R	—	Y
H411N ^{5,20,105}	—	—	—	R	—	Y
H411Y ^{5,18,20,105}	—	—	—	R	—	Y
H520Q ^{12,15,51,80,87,92}	S	S	R	—	—	Y
I610T ^{15,40}	—	—	R	—	—	Y
K355M ^{15,94,100}	—	—	R	R	—	Y
K355del ¹⁰⁰	—	—	R	R	—	Y
K359E ^{20,103}	—	—	R	S	—	Y
K359N ⁹⁹	—	—	R	S	—	Y
K359Q ^{20,103}	—	—	R	S	—	Y
K599E ^{15,81}	—	—	S	—	—	Y
K599M ^{10,80}	—	—	R	—	—	N

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
K599R ^{15,85}	—	—	S	—	—	Y
K599T ^{10,15,106}	S	—	R	—	—	Y
K599del ^{15,81}	—	—	R	—	—	Y
L337M ^{5,20}	—	—	—	R	—	Y
L348V ⁹⁹	—	—	S	R	—	Y
L397R ^{5,20,107}	—	—	S	R	—	Y
L405P ^{15,85}	—	—	R	—	—	Y
L595F ^{10,12,15,80,108}	—	—	R	—	—	Y
L595S ^{12,13,15,51,69,79,80,87,92}	—	—	R	—	—	Y
L595T ^{10,53,80}	S	S	R	—	—	N
L595W ^{10,12,15,80,82,87}	—	—	R	—	—	Y
L595del ^{10,15,79,80,81,109}	—	—	R	—	—	Y
L600I ^{15,85}	—	—	S	—	—	Y
L600del ^{10,12,15,45,80,81,82}	—	—	R	—	—	Y
L634Q ^{15,82}	—	—	S	—	—	Y
M460I ^{12,15,28,51,69,80,87,92,110}	S	S	R	—	—	Y
M460L ^{10,84}	—	—	R	—	—	N
M460T ^{15,85,92}	—	—	R	—	—	Y
M460V ^{12,13,15,36,40,60,79,80,87,90,92}	—	S	R	—	—	Y
M615V ^{15,96}	—	—	S	—	—	Y
N597D ^{15,111}	—	—	S	—	—	Y
N597I ^{10,80}	—	—	R	—	—	N
P521L ^{15,100}	—	—	R	R	—	Y
T409M ^{5,18,20}	—	—	—	R	—	Y
T601M ^{15,81}	—	—	S	—	—	Y
T601del ^{15,81,112}	—	—	R	—	—	Y
V345I ⁹⁹	—	—	S	S	—	Y
V353A ^{3,5,20}	—	—	—	R	—	Y
V356G ^{15,100,101}	—	—	R	R	—	Y
V466G ^{14,15,96,100}	—	—	R	R	—	Y
Y617H ^{15,93}	—	—	S	—	—	Y
Y617del ^{20,94}	—	—	R	R	—	Y

* = stop codon

del = deletion

R = "Resistant." Resistant indicates evidence of drug resistance compared with a wild-type virus.

P = "Possible Resistance." Possible resistance indicates mutations were detected with borderline-level drug resistance or conflicting resistance status reported in the literature.

S = "Sensitive." Ignored by the plugin and reported as additional variant.

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping
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– = No known resistance-association or phenotypically confirmed sensitivity to specified drug. Ignored in the analysis.

Y = "Yes." Mutation's resistance profile was confirmed by marker transfer/phenotyping experiments.

N = "No." Mutation's resistance profile has not been confirmed by marker transfer/phenotyping experiments.

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