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

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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 letermovir.

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**	**Letermovir**	**Confirmed by Phenotyping**	**References**
A269T	–	–	–	P	–	Y	3
A406V	–	–	–	P	–	Y	3, 4
C415*	–	–	–	P	–	Y	3, 4
D534Y	–	–	–	P	–	Y	5
E22*	–	–	–	P	–	Y	3
K89N	–	–	–	S	–	Y	6
L193F	–	–	–	P	–	Y	3
L335P	–	–	–	R	–	Y	3, 7
L426F	–	–	–	P	–	Y	3
R233S	–	–	–	P	–	Y	4,5
R448P	–	–	–	P	–	Y	5
V353E	–	–	–	P	–	Y	3
W153R	–	–	–	P	–	Y	3
W362*	–	–	–	P	–	Y	3
W362R	–	–	–	P	–	Y	4

UL54 Variants							
Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
883-884ins	—	—	—	—	—	N	8
981-982del	R	R	R	—	—	Y	9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19
A505V	P	S	P	—	—	Y	8, 15
A543P	R	S	R	—	—	Y	16, 20
A809V	P	R	R	—	—	Y	10, 11, 12, 15, 19, 21, 22, 23, 24, 25
A834P	R	R	R	—	—	Y	14, 15, 26
A987G	R	S	R	—	—	Y	10, 15, 19, 27, 28, 29, 30
A987V	S	R	S	—	—	Y	18, 19
C524del	R	S	R	—	—	Y	15, 31
C539G	R	S	R	—	—	Y	15, 32
C539R	R	S	R	—	—	Y	33, 34
C590F	S	R	S	—	—	Y	35
D301N	R	S	R	—	—	Y	11, 12, 15, 19
D413A	R	S	R	—	—	Y	14, 15, 36
D413E	R	S	R	—	—	Y	10, 11, 12, 14 15, 28, 37, 38
D413N	R	S	R	—	—	Y	15, 32
D413Y	R	S	R	—	—	Y	15, 39
D515E	P	P	R	—	—	Y	10, 40, 41
D515G	S	S	S	—	—	Y	11
D515Y	P	P	R	—	—	Y	15, 16, 17, 19, 41
D542E	R	S	S	—	—	Y	15, 42
D588E	S	R	S	—	—	Y	10, 28, 30
D588N	P	R	R	—	—	Y	12, 15, 23, 28, 43
D594N	S	S	S	—	—	Y	18
E303D	R	S	R	—	—	Y	15, 39
E303G	R	S	R	—	—	Y	15, 39
E756D	S	R	S	—	—	Y	11, 12, 15
E756G	S	R	S	—	—	Y	44
E756K	P	R	R	—	S	Y	11, 12, 15, 23, 28, 45, 46, 47, 48
E756Q	S	R	S	—	—	Y	12, 15, 21, 49
E951D	S	R	R	—	—	Y	15, 24
E989D	P	R	R	—	—	Y	18
F412C	R	S	R	—	—	Y	10, 12, 15, 19, 30, 50
F412L	R	S	R	—	—	Y	15, 19, 23

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
F412S	R	S	R	—	—	Y	15, 23, 34, 51
F412V	R	S	R	—	—	Y	10, 15, 28, 30
F595I	S	R	S	—	—	Y	15, 33, 34
G841A	R	R	R	—	—	Y	14, 15, 22
G841S	S	P	P	—	—	Y	8
G971D	S	S	S	—	—	Y	11
H600L	R	R	R	—	—	Y	44
I521T	R	S	R	—	—	Y	15, 40, 52
I722V	R	S	R	—	—	N	10
I726T	P	S	P	—	—	Y	8, 15
I726V	R	S	R	—	—	Y	8, 15
K493N	R	R	R	—	—	Y	18
K500N	R	S	R	—	—	Y	15, 33, 34
K513E	R	S	R	—	—	Y	10, 12, 15, 28, 30
K513N	R	S	R	—	—	Y	10, 12, 15, 28, 37, 53, 54
K513Q	R	S	R	—	—	Y	35
K513R	R	S	R	—	—	Y	10, 15, 19, 32
K513T	R	S	R	—	—	Y	18
K805Q	R	S	S	—	—	Y	10, 15, 21, 22, 30
L501F	R	S	R	—	—	Y	10, 28, 35, 37, 51, 55
L501I	R	S	R	—	—	Y	10, 12, 15, 28, 30, 56
L516M	S	S	S	—	—	Y	57
L516P	R	S	R	—	—	Y	17, 19
L516R	R	S	R	—	—	Y	11, 12, 15
L516W	R	S	R	—	—	Y	15, 58
L545F	R	S	R	—	—	Y	35
L545S	R	S	R	—	—	Y	10, 12, 15, 30, 33, 59
L545W	R	S	R	—	—	Y	15, 19, 23, 34
L565V	P	R	P	—	—	Y	18
L773V	R	R	R	—	—	Y	15, 32, 60
L776M	S	R	R	—	—	Y	14, 15, 61
L802M	S	R	P	—	—	Y	12, 14, 15, 21, 28, 30, 33, 43, 50, 59
L802V	S	S	P	—	—	Y	33
L862F	S	S	P	—	—	Y	33
L897P	—	—	S	—	—	Y	62
L957F	S	S	R	—	—	Y	15, 33, 34

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
M393K	R	R	R	—	—	N	10, 63
M393R	R	R	R	—	—	N	10, 63
M844T	S	R	S	—	—	Y	15, 64
M844V	S	R	R	—	—	Y	15, 64
N408D	R	S	R	—	—	Y	10, 12, 15, 19, 28, 30, 33, 59, 65
N408H	R	S	R	—	—	Y	35
N408K	R	S	R	—	—	Y	15, 19, 23, 26, 39
N408S	R	S	R	—	—	Y	15, 31, 66
N410K	R	S	R	—	—	Y	11, 15, 19
N495K	S	R	S	—	—	Y	14, 15, 24, 67
P488R	R	S	R	—	—	Y	32, 33
P497S	R	S	P	—	—	Y	18
P522A	R	S	R	—	—	Y	10, 15, 52
P522S	R	S	R	—	—	Y	10, 15, 19, 23, 30, 52
P522T	R	S	R	—	—	Y	35
P829S	S	S	R	—	—	Y	15, 33, 34
Q578H	R	R	R	—	—	Y	15, 19, 23, 34, 60
Q578L	S	P	P	—	—	Y	8, 15
Q783R	S	P	P	—	—	Y	24
Q807A	—	R	—	—	—	Y	21
R1052C	S	S	S	—	—	Y	68
S290R	S	R	P	—	—	Y	15, 24
S585A	S	R	S	—	—	Y	15, 33, 34
T419M	—	R	S	—	—	N	60
T503A	R	S	R	—	—	Y	35
T503I	R	S	R	—	—	Y	10, 11, 12, 14, 15
T552N	S	R	R	—	—	Y	15, 24, 33, 34
T700A	P	R	S	—	—	Y	10, 12, 15, 19, 21, 25, 30, 69
T813S	R	R	R	—	—	Y	14, 15, 22
T821I	S	R	R	—	—	Y	10, 12, 14, 15, 21, 30
T838A	S	R	S	—	—	Y	14, 15, 43
V526L	R	S	R	—	—	Y	15, 46
V715A	S	R	S	—	—	Y	15, 58
V715M	S	R	S	—	—	Y	10, 12, 15, 21, 25, 30, 49, 69
V781I	S	R	P	—	—	Y	15, 23, 28, 30
V787A	S	R	R	—	—	Y	15, 41, 48

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

UL56 Variants							
Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
A365S	—	—	—	—	R	Y	16, 20
C25F	—	—	—	—	R	Y	16
C325F	—	—	—	—	R	Y	71, 72
C325R	—	—	—	—	R	Y	71, 72
C325W	—	—	—	—	R	Y	16, 72
C325Y	—	—	—	—	R	Y	16, 71, 72, 73
E237D	—	—	—	—	R	Y	71, 72, 74
E237G	S	S	—	—	R	Y	72, 75
F261C	—	—	—	—	R	Y	71, 72
F261L	—	—	—	—	R	Y	71, 72, 74
F261S	—	—	—	—	R	N	72
K258E	—	—	—	—	R	Y	74
L241P	—	—	—	—	R	Y	71, 73, 76, 77
L254F	—	—	—	—	R	Y	20, 77
L257F	—	—	—	—	R	Y	16, 20, 77
L257I	—	—	—	—	R	Y	71, 72
L328V	—	—	—	—	R	Y	16, 20
M329T	—	—	—	—	R	Y	71, 72, 74
N232Y	—	—	—	—	R	Y	74
N368D	—	—	—	—	R	Y	20, 77
Q204R	—	—	—	—	P	Y	74
R369G	—	—	—	—	R	Y	72, 73
R369M	—	—	—	—	R	Y	72, 73, 77
R369S	—	—	—	—	R	Y	72, 73, 76
R369T	S	S	S	—	R	Y	20, 75
S229F	—	—	—	—	R	Y	20, 77
T244K	—	—	—	—	R	Y	71, 72

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

UL97 Variants							
Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
590-593del	S	S	R	—	—	Y	10, 59
590-600del	—	—	R	—	—	N	10, 79
590-603del	—	—	R	—	—	N	10, 37
590-607del	—	—	R	—	—	N	15
591-594del	—	—	R	—	—	Y	10, 12, 80, 81
591-607del	—	—	R	—	—	Y	10, 82
595-603del	—	S	R	—	—	Y	10, 12, 70, 81, 83
597-598del	—	—	R	—	—	Y	15, 81
597-599del	—	—	R	—	—	Y	58, 81
597-603del	—	—	—	—	—	N	51
600-601del	—	—	R	—	—	Y	10, 15, 70, 81
601-602del	—	—	R	—	—	Y	15, 81
601-603del	S	S	R	—	—	Y	36, 81
A590T	—	—	R	—	—	N	10, 80, 84
A591D	—	—	R	—	—	N	10, 80, 84
A591V	—	—	R	—	—	Y	15, 16, 81
A594E	—	—	R	—	—	Y	14, 15, 85
A594G	—	—	R	—	—	Y	15, 66, 86
A594P	—	—	R	—	—	Y	10, 35, 51, 87, 88
A594S	—	—	R	—	—	Y	20, 89
A594T	—	—	R	—	—	Y	12, 15, 45, 58, 80, 82, 90, 91

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
A594V	—	—	R	—	—	Y	12, 13, 15, 51, 69, 79, 80, 81, 87, 90, 92
A606D	—	—	P	—	—	N	10, 80, 84
A613V	—	—	R	—	—	Y	15, 57, 66
A619V	—	—	S	—	—	Y	15, 58
A674T	—	—	S	—	—	Y	15, 93
C480F	—	—	R	R	—	Y	18, 20
C480R	—	—	R	R	—	Y	15, 94
C518Y	—	—	R	—	—	Y	15, 66, 95
C592F	—	—	R	—	—	N	10
C592G	S	S	R	—	—	Y	12, 13, 15, 18, 24, 28, 80, 81, 82, 87, 92
C603R	—	—	R	—	—	Y	14, 15, 92, 96
C603S	—	—	P	—	—	Y	14, 15, 85, 92
C603W	S	S	R	—	—	Y	10, 12, 15, 51, 53, 80, 87, 92
C603Y	—	—	R	—	—	N	10, 80, 84
C607F	—	—	R	—	—	Y	10, 15, 82, 90
C607Y	—	S	R	—	—	Y	9, 12, 15, 51, 80, 82, 97, 98
D456N	—	—	R	R	—	Y	20, 94
D605E	—	—	S	—	—	Y	13, 15, 20
E362D	—	—	R	S	—	Y	99
E596D	—	—	S	—	—	Y	15, 40
E596G	—	—	R	—	—	Y	10, 12, 15, 45, 53, 80, 82
E596Q	—	—	R	—	—	Y	35
E596Y	—	—	R	—	—	Y	15, 40
E596del	—	—	R	—	—	Y	15, 81
E655K	—	—	S	—	—	Y	15, 46
F342S	—	—	R	R	—	Y	15, 100, 101, 102
F342Y	—	—	R	R	—	Y	20, 103
G598S	—	—	R	—	—	Y	10, 12, 104
G598V	—	—	R	—	—	N	10, 84
H411L	—	—	—	R	—	Y	5, 20, 105
H411N	—	—	—	R	—	Y	5, 20, 105
H411Y	—	—	—	R	—	Y	5, 18, 20, 105
H520Q	S	S	R	—	—	Y	12, 15, 51, 80, 87, 92
I610T	—	—	R	—	—	Y	15, 40
K355M	—	—	R	R	—	Y	15, 94, 100

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
K355del	—	—	R	R	—	Y	100
K359E	—	—	R	S	—	Y	20, 103
K359N	—	—	R	S	—	Y	99
K359Q	—	—	R	S	—	Y	20, 103
K599E	—	—	S	—	—	Y	15, 81
K599M	—	—	R	—	—	N	10, 80
K599R	—	—	S	—	—	Y	15, 85
K599T	S	—	R	—	—	Y	10, 15, 106
K599del	—	—	R	—	—	Y	15, 81
L337M	—	—	—	R	—	Y	5, 20
L348V	—	—	S	R	—	Y	99
L397R	—	—	S	R	—	Y	5, 20, 107
L405P	—	—	R	—	—	Y	15, 85
L595F	—	—	R	—	—	Y	10, 12, 15, 80, 108
L595S	—	—	R	—	—	Y	12, 13, 15, 51, 69, 79, 80, 87, 92
L595T	S	S	R	—	—	N	10, 53, 80
L595W	—	—	R	—	—	Y	10, 12, 15, 80, 82, 87
L595del	—	—	R	—	—	Y	10, 15, 79, 80, 81, 109
L600I	—	—	S	—	—	Y	15, 85
L600del	—	—	R	—	—	Y	10, 12, 15, 45, 80, 81, 82
L634Q	—	—	S	—	—	Y	15, 82
M460I	S	S	R	—	—	Y	12, 15, 28, 51, 69, 80, 87, 92, 110
M460L	—	—	R	—	—	N	10, 84
M460T	—	—	R	—	—	Y	15, 85, 92
M460V	—	S	R	—	—	Y	12, 13, 15, 36, 40, 60, 79, 80, 87, 90, 92
M615V	—	—	S	—	—	Y	15, 96
N597D	—	—	S	—	—	Y	15, 111
N597I	—	—	R	—	—	N	10, 80
P521L	—	—	R	R	—	Y	15, 100
T409M	—	—	—	R	—	Y	5, 18, 20
T601M	—	—	S	—	—	Y	15, 81
T601del	—	—	R	—	—	Y	15, 81, 11s
V345I	—	—	S	S	—	Y	99
V353A	—	—	—	R	—	Y	3, 5, 20
V356G	—	—	R	R	—	Y	15, 100, 101
V466G	—	—	R	R	—	Y	14, 15, 96, 100

Variant	Cidovir	Foscarnet	Ganciclovir	Maribavir	Letermovir	Confirmed by Phenotyping	References
Y617H	—	—	S	—	—	Y	15, 93
Y617del	—	—	R	R	—	Y	20, 94

* = 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.

— = 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.

Table References

3. Chou et al. 2008. Diverse cytomegalovirus UL27 mutations adapt to loss of viral UL97 kinase activity under maribavir. Antimicrobial agents and chemotherapy. PMID:18981262.	4. Chou et al. 2004. Mutations in the human cytomegalovirus UL27 gene that confer resistance to maribavir. Journal of virology. PMID:15194788.
5. Chou et al. 2012. Effects on maribavir susceptibility of cytomegalovirus UL97 kinase ATP binding region mutations detected after drug exposure in vitro and in vivo. Antiviral research. PMID:22664236.	6. Hakki et al. 2011. Resistance to maribavir is associated with the exclusion of pUL27 from nucleoli during human cytomegalovirus infection. Antiviral research. PMID:21906628.
7. Komazin et al. 2003. Resistance of human cytomegalovirus to the benzimidazole L-ribonucleoside maribavir maps to UL27. Journal of virology. PMID:14557635.	8. Chou et al. 2013. Phenotypic evaluation of previously uncharacterized cytomegalovirus DNA polymerase sequence variants detected in a valganciclovir treatment trial. The Journal of infectious diseases. PMID:24273181.
9. Chou et al. 2000. A deletion mutation in region V of the cytomegalovirus DNA polymerase sequence confers multidrug resistance. The Journal of infectious diseases. PMID:11069251.	10. Gilbert et al. 2002. Resistance of herpesviruses to antiviral drugs: clinical impacts and molecular mechanisms. Drug resistance updates: reviews and commentaries in antimicrobial and anticancer chemotherapy. PMID:12135584.
11. Chou et al. 2003. Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. The Journal of infectious diseases. PMID:12825168.	12. Baldanti et al. 2004. Clinical and biologic aspects of human cytomegalovirus resistance to antiviral drugs. Human immunology. PMID:15172438.
13. Chou et al. 2005. Phenotyping of cytomegalovirus drug resistance mutations by using recombinant viruses incorporating a reporter gene. Antimicrobial agents and chemotherapy. PMID:15980340.	14. Lurain et al. 2010. Antiviral drug resistance of human cytomegalovirus. Clinical microbiology reviews. PMID:20930070.
15. Kotton et al. 2018. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. PMID:29596116.	16. Chou et al. 2018. New Locus of Drug Resistance in the Human Cytomegalovirus UL56 Gene Revealed by . Antimicrobial agents and chemotherapy. PMID:29914965.
17. Cherrier et al. 2018. Emergence of letermovir resistance in a lung transplant recipient with ganciclovir-resistant cytomegalovirus infection. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. PMID:30286286.	18. Chou et al. 2020. Drug Resistance Mutations and Associated Phenotypes Detected in Clinical Trials of Maribavir for Treatment of Cytomegalovirus Infection. The Journal of infectious diseases. PMID:32726419.
19. Chou et al. 2021. Opposite effects of cytomegalovirus UL54 exonuclease domain mutations on acyclovir and cidofovir susceptibility. Antiviral research. PMID:34560144.	20. Chou et al. 2020. Advances in the genotypic diagnosis of cytomegalovirus antiviral drug resistance. Antiviral research. PMID:31940472.
21. Tchesnokov et al. 2006. Role of helix P of the human cytomegalovirus DNA polymerase in resistance and hypersusceptibility to the antiviral drug foscarnet. Journal of virology. PMID:16415021.	22. Chou et al. 2007. Growth and drug resistance phenotypes resulting from cytomegalovirus DNA polymerase region III mutations observed in clinical specimens. Antimicrobial agents and chemotherapy. PMID:17709468.
23. Chou et al. 2011. Phenotypic diversity of cytomegalovirus DNA polymerase gene variants observed after antiviral therapy. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:21295516.	24. Chou et al. 2016. Foscarnet resistance mutations mapping to atypical domains of the cytomegalovirus DNA polymerase gene. Antiviral research. PMID:27940027.
25. Chou et al. 1998. Mutation in region III of the DNA polymerase gene conferring foscarnet resistance in cytomegalovirus isolates from 3 subjects receiving prolonged antiviral therapy. The Journal of infectious diseases. PMID:9697736.	26. Scott et al. 2006. Multidrug resistance conferred by novel DNA polymerase mutations in human cytomegalovirus isolates. Antimicrobial agents and chemotherapy. PMID:17043128.
27. Chou et al. 1999. Interstrain variation in the human cytomegalovirus DNA polymerase sequence and its effect on genotypic diagnosis of antiviral drug resistance. Adult AIDS Clinical Trials Group CMV Laboratories. Antimicrobial agents and chemotherapy. PMID:10348781.	28. Mousavi-Jazi et al. 2001. Variations in the cytomegalovirus DNA polymerase and phosphotransferase genes in relation to foscarnet and ganciclovir sensitivity. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:11595579.
29. Sullivan et al. 1993. A point mutation in the human cytomegalovirus DNA polymerase gene confers resistance to ganciclovir and phosphonylmethoxyalkyl derivatives. Antimicrobial agents and chemotherapy. PMID:8381637.	30. Cihlar et al. 1998. Characterization of drug resistance-associated mutations in the human cytomegalovirus DNA polymerase gene by using recombinant mutant viruses generated from overlapping DNA fragments. Journal of virology. PMID:9621055.
31. Hantz et al. 2013. Novel DNA polymerase mutations conferring cytomegalovirus resistance: input of BAC-recombinant phenotyping and 3D model. Antiviral research. PMID:23415883.	32. Chou et al. 2014. Improved detection of emerging drug-resistant mutant cytomegalovirus subpopulations by deep sequencing. Antimicrobial agents and chemotherapy. PMID:24890586.

33. Gilbert et al. 2011. Recombinant phenotyping of cytomegalovirus UL54 mutations that emerged during cell passages in the presence of either ganciclovir or foscarnet. Antimicrobial agents and chemotherapy. PMID:21709106.

34. Hakki et al. 2011. The biology of cytomegalovirus drug resistance. Current opinion in infectious diseases. PMID:22001948.

35. Chou et al. 2023. Drug Resistance Assessed in a Phase 3 Clinical Trial of Maribavir Therapy for Refractory or Resistant Cytomegalovirus Infection in Transplant Recipients. The Journal of infectious diseases. PMID:37506264.

36. Marfori et al. 2006. Development of new cytomegalovirus UL97 and DNA polymerase mutations conferring drug resistance after valganciclovir therapy in allogeneic stem cell recipients. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:17157554.

37. Emery et al. 2001. Progress in understanding cytomegalovirus drug resistance. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:11397658.

38. Seo et al. 2001. Cytomegalovirus ventriculoencephalitis in a bone marrow transplant recipient receiving antiviral maintenance: clinical and molecular evidence of drug resistance. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. PMID:11577375.

39. Chou et al. 2016. Novel Cytomegalovirus UL54 DNA Polymerase Gene Mutations Selected In Vitro That Confer Brincidofovir Resistance. Antimicrobial agents and chemotherapy. PMID:27044553.

40. Fischer et al. 2015. Identification of newly detected, drug-related HCMV UL97- and UL54-mutations using a modified plaque reduction assay. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:26209398.

41. Andouard et al. 2016. Contrasting effect of new HCMV pUL54 mutations on antiviral drug susceptibility: Benefits and limits of 3D analysis. Antiviral research. PMID:26872863.

42. James et al. 2013. Selection and recombinant phenotyping of a novel CMX001 and cidofovir resistance mutation in human cytomegalovirus. Antimicrobial agents and chemotherapy. PMID:23650158.

43. Springer et al. 2005. How evolution of mutations conferring drug resistance affects viral dynamics and clinical outcomes of cytomegalovirus-infected hematopoietic cell transplant recipients. Journal of clinical microbiology. PMID:15634973.

44. Park et al. 2022. Analysis of Novel Drug-Resistant Human Cytomegalovirus DNA Polymerase Mutations Reveals the Role of a DNA-Binding Loop in Phosphonoformic Acid Resistance. Frontiers in microbiology. PMID:35185843.

45. Gilbert et al. 2005. Human cytomegalovirus resistance to antiviral drugs. Antimicrobial agents and chemotherapy. PMID:15728878.

46. Drouot et al. 2014. Characterization of multiple cytomegalovirus drug resistance mutations detected in a hematopoietic stem cell transplant recipient by recombinant phenotyping. Journal of clinical microbiology. PMID:25143583.

47. Piret et al. 2017. Drug Susceptibility and Replicative Capacity of Multidrug-Resistant Recombinant Human Cytomegalovirus Harboring Mutations in Antimicrobial agents and chemotherapy. PMID:28807919.

48. Piret et al. 2019. Compartmentalization of a Multidrug-Resistant Cytomegalovirus UL54 Mutant in a Stem Cell Transplant Recipient with Encephalitis. The Journal of infectious diseases. PMID:31199457.

49. Weinberg et al. 2003. Mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. The Journal of infectious diseases. PMID:12599051.

50. Chou et al. 1997. Evolution of mutations conferring multidrug resistance during prophylaxis and therapy for cytomegalovirus disease. The Journal of infectious diseases. PMID:9291334.

51. Lurain et al. 2002. Analysis and characterization of antiviral drug-resistant cytomegalovirus isolates from solid organ transplant recipients. The Journal of infectious diseases. PMID:12198609.

52. Chou et al. 2008. Contrasting drug resistance phenotypes resulting from cytomegalovirus DNA polymerase mutations at the same exonuclease locus. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:18502683.

53. Smith et al. 1997. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. The Journal of infectious diseases. PMID:9207351.

54. Cihlar et al. 1998. A point mutation in the human cytomegalovirus DNA polymerase gene selected in vitro by cidofovir confers a slow replication phenotype in cell culture. Virology. PMID:9721246.

55. Harada et al. 1997. Genetic analysis of a clinical isolate of human cytomegalovirus exhibiting resistance against both ganciclovir and cidofovir. Archives of virology. PMID:9125039.

56. Lurain et al. 1992. Point mutations in the DNA polymerase gene of human cytomegalovirus that result in resistance to antiviral agents. Journal of virology. PMID:1331515.

57. Fischer et al. 2013. Generation and characterization of a GCV resistant HCMV UL97-mutation and a drug sensitive UL54-mutation. Antiviral research. PMID:24120366.

58. Fischer et al. 2016. Identification of resistance-associated HCMV UL97- and UL54-mutations and a UL97- polymporphism with impact on phenotypic drug-resistance. Antiviral research. PMID:27058773.

59. Gilbert et al. 2005. New reporter cell line to evaluate the sequential emergence of multiple human cytomegalovirus mutations during in vitro drug exposure. Antimicrobial agents and chemotherapy. PMID:16304146.

60. Mousavi-Jazi et al. 2003. Point mutations induced by foscarnet PFA in the human cytomegalovirus DNA polymerase. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:12637079.

61. Shapira et al. 2008. Artesunate as a potent antiviral agent in a patient with late drug-resistant cytomegalovirus infection after hematopoietic stem cell transplantation. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. PMID:18419454.

62. Chou et al. 2010. Recombinant phenotyping of cytomegalovirus sequence variants detected after 200 or 100 days of valganciclovir prophylaxis. Transplantation. PMID:21030903.

63. Cherrington et al. 1998. In vitro antiviral susceptibilities of isolates from cytomegalovirus retinitis patients receiving first- or second-line cidofovir therapy: relationship to clinical outcome. The Journal of infectious diseases. PMID:9815243.

64. Chou et al. 2011. Cyclopropavir susceptibility of cytomegalovirus DNA polymerase mutants selected after antiviral drug exposure. Antimicrobial agents and chemotherapy. PMID:21968367.

65. Erice et al. 1997. Antiviral susceptibilities and analysis of UL97 and DNA polymerase sequences of clinical cytomegalovirus isolates from immunocompromised patients. The Journal of infectious diseases. PMID:9129070.

66. Göhring et al. 2015. Antiviral Drug- and Multidrug Resistance in Cytomegalovirus Infected SCT Patients. Computational and structural biotechnology journal. PMID:25750703.

67. Ducancelle et al. 2006. A novel mutation in the UL54 gene of human cytomegalovirus isolates that confers resistance to foscarnet. Antiviral therapy. PMID:16856628.

68. Lanier et al. 2016. Analysis of Mutations in the Gene Encoding Cytomegalovirus DNA Polymerase in a Phase 2 Clinical Trial of Brincidofovir Prophylaxis. The Journal of infectious diseases. PMID:26941282.

69. Baldanti et al. 1996. Single amino acid changes in the DNA polymerase confer foscarnet resistance and slow growth phenotype, while mutations in the UL97-encoded phosphotransferase confer ganciclovir resistance in three double-resistant human cytomegalovirus strains recovered from patients with AIDS. Journal of virology. PMID:8627655.

70. Jabs et al. 2000. Mutations conferring ganciclovir resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. The Journal of infectious diseases. PMID:11120934.

71. Chou et al. 2015. Rapid In Vitro Evolution of Human Cytomegalovirus UL56 Mutations That Confer Letermovir Resistance. Antimicrobial agents and chemotherapy. PMID:26259791.

72. Premyvis [Prescribing information]. U.S. Food and Drug Administration. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939Orig1s000,209940Orig1s000lb

73. Goldner et al. 2013. Geno- and phenotypic characterization of human cytomegalovirus mutants selected in vitro after letermovir AIC246 exposure. Antimicrobial agents and chemotherapy. PMID:24189264.

74. Chou et al. 2017. Comparison of Cytomegalovirus Terminase Gene Mutations Selected after Exposure to Three Distinct Inhibitor Compounds. Antimicrobial agents and chemotherapy. PMID:28827420.

75. Douglas et al. 2019. Letermovir Resistance Analysis in a Clinical Trial of Cytomegalovirus Prophylaxis for Hematopoietic Stem Cell Transplant Recipients. The Journal of infectious diseases. PMID:31781762.

76. Goldner et al. 2011. The novel anticytomegalovirus compound AIC246 Letermovir inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. Journal of virology. PMID:21752907.

77. Chou et al. 2017. A third component of the human cytomegalovirus terminase complex is involved in letermovir resistance. Antiviral research. PMID:29107686.

78. Lischka et al. 2015. Characterization of Cytomegalovirus Breakthrough Events in a Phase 2 Prophylaxis Trial of Letermovir AIC246, MK 8228. The Journal of infectious diseases. PMID:26113373.

79. Wolf et al. 2001. Emergence of multiple human cytomegalovirus ganciclovir-resistant mutants with deletions and substitutions within the UL97 gene in a patient with severe combined immunodeficiency. Antimicrobial agents and chemotherapy. PMID:11158760.

80. Erice et al. 1999. Resistance of human cytomegalovirus to antiviral drugs. Clinical microbiology reviews. PMID:10194460.

81. Chou et al. 2017. Differentiated Levels of Ganciclovir Resistance Conferred by Mutations at Codons 591 to 603 of the Cytomegalovirus UL97 Kinase Gene. Journal of clinical microbiology. PMID:28446569.

82. Chou et al. 2002. Cytomegalovirus UL97 phosphotransferase mutations that affect susceptibility to ganciclovir. The Journal of infectious diseases. PMID:11807689.

83. Chou et al. 1999. A nine-codon deletion mutation in the cytomegalovirus UL97 phosphotransferase gene confers resistance to ganciclovir. Antimicrobial agents and chemotherapy. PMID:10602745.

84. Wolf et al. 1998. Early emergence of ganciclovir-resistant human cytomegalovirus strains in children with primary combined immunodeficiency. The Journal of infectious diseases. PMID:9697738.

85. Chou et al. 2010. Recombinant phenotyping of cytomegalovirus UL97 kinase sequence variants for ganciclovir resistance. Antimicrobial agents and chemotherapy. PMID:20385869.

86. Bourgeois et al. 1997. Value of a ligase chain reaction assay for detection of ganciclovir resistance-related mutation 594 in UL97 gene of human cytomegalovirus. Journal of virological methods. PMID:9300382.

87. Lurain et al. 2001. Sequencing of cytomegalovirus UL97 gene for genotypic antiviral resistance testing. Antimicrobial agents and chemotherapy. PMID:11557468.

88. Ijichi et al. 2001. GCV resistance due to the mutation A594P in the cytomegalovirus protein UL97 is partially reconstituted by a second mutation at D605E. Antiviral research. PMID:11750939.

89. Wong et al. 2019. Patient-Derived Cytomegaloviruses with Different Ganciclovir Sensitivities from UL97 Mutation Retain Their Replication Efficiency and Some Kinase Activity. Antimicrobial agents and chemotherapy. PMID:31262766.

90. Boivin et al. 2001. Rate of emergence of cytomegalovirus CMV mutations in leukocytes of patients with acquired immunodeficiency syndrome who are receiving valganciclovir as induction and maintenance therapy for CMV retinitis. The Journal of infectious diseases. PMID:11740736.

91. Baldanti et al. 2002. Emergence of multiple drug-resistant human cytomegalovirus variants in 2 patients with human immunodeficiency virus infection unresponsive to highly active antiretroviral therapy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. PMID:11915006.

92. Chou et al. 2010. Cytomegalovirus UL97 mutations affecting cyclopropavir and ganciclovir susceptibility. Antimicrobial agents and chemotherapy. PMID:21041510.

93. Martin et al. 2006. Characterization of human cytomegalovirus HCMV UL97 mutations found in a valganciclovir/oral ganciclovir prophylactic trial by use of a bacterial artificial chromosome containing the HCMV genome. The Journal of infectious diseases. PMID:16897654.

94. Komazin-Meredith et al. 2013. Human cytomegalovirus UL97 kinase is involved in the mechanism of action of methylenecyclopropane analogs with 6-ether and -thioether substitutions. Antimicrobial agents and chemotherapy. PMID:24145545.

95. Zhang et al. 2012. A new mutation in the human cytomegalovirus UL97 gene may confer ganciclovir resistance in Chinese kidney transplant recipients. Archives of virology. PMID:23011309.

96. Martin et al. 2010. Incidence and characterization of cytomegalovirus resistance mutations among pediatric solid organ transplant patients who received valganciclovir prophylaxis. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. PMID:20138805.

97. Smith et al. 1998. Clinical failure of CMV retinitis with intravitreal cidofovir is associated with antiviral resistance. Archives of ophthalmology Chicago, Ill.: 1960. PMID:9488269.

98. Baldanti et al. 1998. The Cys607-->Tyr change in the UL97 phosphotransferase confers ganciclovir resistance to two human cytomegalovirus strains recovered from two immunocompromised patients. Antimicrobial agents and chemotherapy. PMID:9527804.

99. Chou et al. 2021. Ganciclovir and maribavir susceptibility phenotypes of cytomegalovirus UL97 ATP binding region mutations detected by expanded genotypic testing. Antiviral research. PMID:34273445.

100. Chou et al. 2013. Cytomegalovirus UL97 kinase catalytic domain mutations that confer multidrug resistance. Antimicrobial agents and chemotherapy. PMID:23650173.

101. Chou et al. 2015. Approach to drug-resistant cytomegalovirus in transplant recipients. Current opinion in infectious diseases. PMID:26098499.

102. Campos et al. 2016. Human cytomegalovirus antiviral drug resistance in hematopoietic stem cell transplantation: current state of the art. Reviews in medical virology. PMID:26990717.

103. Chou et al. 2019. Novel UL97 drug resistance mutations identified at baseline in a clinical trial of maribavir for resistant or refractory cytomegalovirus infection. Antiviral research. PMID:31568799.

104. Baldanti et al. 2002. Mutations in the UL97 ORF of ganciclovir-resistant clinical cytomegalovirus isolates differentially affect GCV phosphorylation as determined in a recombinant vaccinia virus system. Antiviral research. PMID:11888658.

105. Chou et al. 2007. Accelerated evolution of maribavir resistance in a cytomegalovirus exonuclease domain II mutant. Journal of virology. PMID:17942550.

106. Faizi Khan et al. 1998. Genetic analysis of a ganciclovir-resistant human cytomegalovirus mutant. Antiviral research. PMID:9864050.

107. Biron et al. 2002. Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action. Antimicrobial agents and chemotherapy. PMID:12121906.

108. Wolf et al. 1995. Mutations in human cytomegalovirus UL97 gene confer clinical resistance to ganciclovir and can be detected directly in patient plasma. The Journal of clinical investigation. PMID:7814623.

109. Baldanti et al. 1995. A three-nucleotide deletion in the UL97 open reading frame is responsible for the ganciclovir resistance of a human cytomegalovirus clinical isolate. Journal of virology. PMID:7815545.

110. Lurain et al. 1994. Mutation in the UL97 open reading frame of human cytomegalovirus strains resistant to ganciclovir. Journal of virology. PMID:8207815.

111. Iwasenko et al. 2009. Successful valganciclovir treatment of post-transplant cytomegalovirus infection in the presence of UL97 mutation N597D. Journal of medical virology. PMID:19152402.

112. Hantz et al. 2005. Early selection of a new UL97 mutant with a severe defect of ganciclovir phosphorylation after valaciclovir prophylaxis and short-term ganciclovir therapy in a renal transplant recipient. Antimicrobial agents and chemotherapy. PMID:15793144

References

1. Centers for Disease Control and Prevention. Clinical overview of CMV and congenital CMV. Last reviewed Nov 2024; accessed Apr 2025.

2. López-Aladid R, Guiu A, Mosquera MM, et al. Improvement in detecting cytomegalovirus drug resistance mutations in solid organ transplant recipients with suspected resistance using next generation sequencing. *PLoS One*. 2019;14(7):e0219701.

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