



CMV Resistance Sequencing

TEST CODES:
33125, 33126,
30722

CPT CODE:
87910 (with Multiplier)

CATEGORY
Infectious Disease

Reportable Mutations - UL54 (DNA Polymerase)¹

Viral Phenotype Confirmed by Marker Transfer ²				
Mutation	Cidofovir	Foscarnet	Ganciclovir	REFERENCE
S290R	S	R	S	106
D301N	R	S	R	19,33,56
E303D ⁴	R	S	R	93
E303G ⁴	R	S	R	93
N408D	R	S	R	9,12,23,31,33,35,56,72
N408K ⁴	R	S	R	13,74,93
N408S	R	S	R	84,88
N408H	R	R	R	123
N410K	R	S	R	19,23
F412C	R	S	R	9,20,23,33,35,65,72
F412L	R	S	R	74,111
F412S	R	S	R	25,74,111
F412V	R	S	R	9,23,72
D413A	R	S	R	69,73
D413E	R	S	R	19,23,31,33,52,56,69,72,73
D413N	R	S	R	89
D413Y ⁴	R	S	R	93
P488R	R	S	R	79,111
K493N	R	R	R	118
N495K	S	R	S	73,76,106
P497S	R	S	S	118
K500N	R	S	R	79,11
L501I	R	S	R	2,9,12,23,33,64,72
T503I	R	S	R	12,19,33,35,72,73
T503A	R	S	R	123
K513N	R	S	R	23,33,35,56,72
K513E	R	S	R	9,23,33,34,35,72
K513R	R	S	R	35,72,89
K513T	R	S	R	118
K513Q	R	S	R	123
D515E	S	S	R	90
D515Y	R	S	R	91,121
L516P	R	S	R	120
L516R	R	S	R	19,33
L516W	R	S	R	92

¹ Most UL54 mutations also have UL97 mutations.

² R and S denote resistant and sensitive, respectively. ND indicates Not Determined.

³ Low-grade or variable resistance.

⁴ Also confers resistance to CMX001.

Reportable Mutations - UL54 (DNA Polymerase)¹

Viral Phenotype Confirmed by Marker Transfer ²				
Mutation	Cidofovir	Foscarnet	Ganciclovir	REFERENCE
I521T	R	S	R	66,68,72
P522A	R	S	R	33,37,68,72
P522S	R	S	R	68,72
P522T	R	S	R	123
del524	R	S	R	88
V526L	R	S	R	82
C539G	R	S	R	89
C539R	R	S	R	79,111
D542E ⁴	R	S	S	81
A543P	R	S	R	108
L545S	R	S	R	9,12,33,72
L545W	R	S	R	74,111
L545F	R	S	R	123
T552N	S	R	R	79,106,111
L565V	S	R	S	118
Q578H	R	R	R	24,74,111
Q578L	S	R	S	83
S585A	S	R	S	79,111
D588E	S	R	S	9,12,23,35,72
D588N	S	R	R	12,23,27,33,74
C590F	S	R	S	123
F595I	S	R	S	79,111
T700A	S	R	S	5,9,18,33,47,72
V715A	S	R	S	92
V715M	S	R	S	5,9,18,25,33,37,47,72,92
I726T	S	S	R	83
E756K	R or S ³	R	R	12,19,23,33,36,74, 82,110
E756D	S	R	S	12,19,31,33
E756Q	S	R	S	12,18,33,37
L773V	R	R	R	24,89
L776M	S	R	R	67,73
V781I	S	R	R ³	9,23,74
V787A	S	R	R	91
V787L	S	R	R	18,37,48,73
L802M	S	R	R or S ³	9,12,18,20,23,27,33,35,65,73
K805Q	R	S	S	9,18,28,35,72
A809V	S	R	R	18,25,28,33,47,72,106
V812L ⁴	R	R	R	12,18,20,27,28,33,72,73,78,93
T813S	R	R	R	28,73
T821I	S	R	R	9,18,28,33,35,72,73
V823A	R	S	R	118
P829S	S	S	R	79,111

¹ Most UL54 mutations also have UL97 mutations.

² R and S denote resistant and sensitive, respectively. ND indicates Not Determined.

³ Low-grade or variable resistance

⁴ Also confers resistance to CMX001.

Reportable Mutations - UL54 (DNA Polymerase)¹

Viral Phenotype Confirmed by Marker Transfer ²				
Mutation	Cidofovir	Foscarnet	Ganciclovir	REFERENCE
A834P	R	R	R	13,73
T838A	S	R	S	27,28,73
G841A	R	R	R	28,72,73
G841S	S	R	R	83
V946L	S	R	S	79,111
E951D	S	R	R	106
L957F	ND	ND	R	79,111
del981 to 982	R	R	R	11,19,33,63,72,73,108
A987G	R	S	R	1,9,22,23,25,43,72
A987V	S	R	S	118
E989D	S	R	R	118
N495K+Q783R	S	R	R	106

Reportable Mutations - UL54 (DNA Polymerase)¹

Viral Phenotype found in Clinical Isolates (Unconfirmed by Marker Transfer) ²				
Mutation	Cidofovir	Foscarnet	Ganciclovir	REFERENCE
M393R	R	R	R	20,72
M393K	R	R	R	20,72
T419M	S	R	S	24
L501F	R	S	R	23,25,31,56,72
Y(I)722V	R	S	R	35,72
H729Y	S	R	S	115
Y751H	R	S	R	35,72
V787I	S	R	S	33

¹ Most UL54 mutations also have UL97 mutations.

² R and S denote resistant and sensitive, respectively. ND indicates Not Determined.

³ Low-grade or variable resistance.

⁴ Also confers resistance to CMX001.

Reportable Mutations - UL56 (Terminase)

Viral Phenotype Confirmed by Marker Transfer ¹		
Mutation	Letermovir	REFERENCE
S229F	R	104
V231A	R	102
V231L	R	98,102,104,108
N232Y	R	105
V236A	R	108
V236L	R	102
V236M	R	97,98,104,110
E237D	R	102,105
E237G	R	122
L241P	R	98,102,103,104
T244K	R	102
L254F	R	104
L257F	R	104
L257I	R	102,104
K258E	R	105
F261L	R	102,104,105
Y321C	R	102
C325F	R	102
C325W	R	108
C325R	R	102
C325Y	R	98,102
M329T	R	102,105
A365S	R	108
N368D	R	104
R369G	R	98
R369M	R	98,104
R369S	R	98,103
R369T	R	122
E237D, T244K, F261L	R	102
V236L, L257I	R	102
V236M, L257I, M329T	R	102
S229F, L254F, L257I	R	104

¹ R denotes resistance.

Reportable Mutations - UL97 (Phosphotransferase)

Viral Phenotype Confirmed by Marker Transfer ¹			
Mutation	Maribavir	Ganciclovir	REFERENCE
F342S	ND	R	94,95,96
F342Y	R	R	112,114
V356G	ND	R	95,96
K359E	ND	R	112,114
K359Q	ND	R	112,114
K359N	ND	R	114,116
E362D	ND	R	116
L405P	ND	R	75
T409M	R	ND	114,119
H411L	R	ND	117,118
H411N	R	ND	117
H411Y	R	ND	114,117
M460I	ND	R	3,5,6,7,8,10,12,23,25,33,109
M460T	ND	R	75,109
M460V	ND	R	6,7,8,10,11,17,24,33,43,50,109
V466G	R	R	73,77,96
C480F	R	R	112,118
C518Y	ND	R	84,85
H520Q	ND	R	6,7,10,25,33,43,109
P521L	R	R	96,112
del590 to 593	ND	R	12,72
del591 to 594	ND	R	8,10,33,34,35,72,107
del591 to 607	ND	R	51,72
A591V	ND	R	107
C592G	ND	R ²	6,8,10,11,20,23,27,33,51,106,107,109,114
A594E	ND	R	73,75
A594G	ND	R	84,86
A594P	ND	R	6,25,59,72
A594T	ND	R	10,25,33,36,50,51,54,92
A594V	ND	R	5,6,8,10,11,17,25,27,33,50,107,109,113
A594S	ND	R	113
L595F	ND	R	10,33,41,72
L595S	ND	R	5,6,8,10,11,12,17,23,25,33,109
L595W	ND	R	6,10,25,33,51,72
del595	ND	R	4,10,17,72,107
del595 to 603	ND	R	14,33,48,72,107
del596	ND	R	107
E596G	ND	R	10,20,33,35,36,51,72
E596Y	ND	R	90
E596Q	-	R	123
del597 to 599	ND	R	92,107

¹ R denotes resistance. ND indicates Not Determined.

² Alone confers modest resistance. When found in conjunction with UL54 del 981 to 982, there is a much higher level of resistance.

Reportable Mutations - UL97 (Phosphotransferase)

Viral Phenotype Confirmed by Marker Transfer ¹			
Mutation	Maribavir	Ganciclovir	REFERENCE
del597 to 598	ND	R	107
G598S	ND	R	33,58,72
del599	ND	R	107
k599T	ND	R	60,72
del600	ND	R	10,33,36,51,72,107
del600-601	ND	R	107
del601	ND	R	107
del601-602	ND	R	107
del601 to 603	ND	R	69,107
C603R	ND	R	73,77,109
C603W	ND	R	6,8,10,20,23,25,33,35,72,109
C607F	ND	R	8,50,51,72
C607Y	ND	R	10,25,33,34,35,39,51,72
I610T	ND	R	90
A613V	ND	R	84,87

¹ R denotes resistance. ND indicates Not Determined.

² Alone confers modest resistance. When found in conjunction with UL54 del 981 to 982, there is a much higher level of resistance.

Reportable Mutations - UL97 (Phosphotransferase)

Viral Phenotype found in Clinical Isolates (Unconfirmed by Marker Transfer) ¹			
Mutation	Maribavir	Ganciclovir	REFERENCE
M460L	ND	R	49,72
A590T	ND	R	10,49,72
del590 to 600	ND	R	17,72
del590 to 603	ND	R	56,72
A591D	ND	R	10,49,72
C592F	ND	R	72
del594 to 601	ND	R	unpublished clinical isolate
L595T	ND	R	10,35,72
N597I	ND	R	10,49,72
del597 to 603	ND	R	25
G598V	ND	R	10,49,72
K599M	ND	R	10,49,72
C603Y	ND	R	6,10,49,72
A606D	ND	R	10,49,72

¹ R denotes resistance. ND indicates Not Determined.

² Alone confers modest resistance. When found in conjunction with UL54 del 981 to 982, there is a much higher level of resistance. For the most up to date list of assays, please visit our website at www.Eurofins-Viracor.com. This test was developed and its performance characteristics determined by Eurofins Viracor. It has not been cleared or approved by the U.S. Food and Drug Administration.

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1. Sullivan V, Biron KK, Talarico C, et al. A point mutation in the human cytomegalovirus DNA polymerase gene confers resistance to ganciclovir and phosphonylmethoxyalkyl derivatives. *Antimicrob Agents Chemother.* 1993 Jan;37(1):19-25.
2. Lurain NS, Thompson KD, Holmes EW, Read GS. Point mutations in the DNA polymerase gene of human cytomegalovirus that result in resistance to antiviral agents. *J Virol.* 1992 Dec;66(12):7146-52.
3. Lurain NS, Spafford LE, Thompson KD. Mutation in the UL97 open reading frame of human cytomegalovirus strains resistant to ganciclovir. *J Virol.* 1994 Jul;68(7):4427-31.
4. Baldanti F, Silini E, Sarasini A, et al. A three-nucleotide deletion in the UL97 open reading frame is responsible for the ganciclovir resistance of a human cytomegalovirus clinical isolate. *J Virol.* 1995 Feb;69(2):796-800.
5. Baldanti F, Underwood MR, Stanat SC, et al. 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. *J Virol.* 1996 Mar;70(3):1390-5.
6. Lurain NS, Weinberg A, Crumpacker CS, et al. Sequencing of cytomegalovirus UL97 gene for genotypic antiviral resistance testing. *Antimicrob Agents Chemother.* 2001 Oct;45(10):2775-80.
7. Gohring K, Mikeler E, Jahn G, Hamprecht K. Rapid simultaneous detection by real-time PCR of cytomegalovirus UL97 mutations in codons 460 and 520 conferring ganciclovir resistance. *J Clin Microbiol.* 2006;44(12):4541-44.
8. Castor J, Cook L, Corey L, Jerome KR. Rapid detection directly from patient serum samples of human cytomegalovirus UL97 mutations conferring ganciclovir resistance. *J Clin Microbiol.* 2007;45(8):2681-83.
9. Cihlar T, Fuller MD, Cherrington JM. Characterization of drug resistance-associated mutations in the human cytomegalovirus DNA polymerase gene by using recombinant mutant viruses generated from overlapping DNA fragments. *J Virol.* 1998;72(7):5927-36.
10. Erice A. Resistance of human cytomegalovirus to antiviral drugs. *Clin Microbiol Rev.* 1999;12(2):286-297.
11. Chou S, Van Wechel LC, Lichy HM, Marousek GI. Phenotyping of cytomegalovirus drug resistance mutations by using recombinant viruses incorporating a reporter gene. *Antimicrob Agents Chemother.* 2005;49(7):2710-15.
12. Gilbert C, Boivin G. New reporter cell line to evaluate the sequential emergence of multiple human cytomegalovirus mutations during in vitro drug exposure. *Antimicrob Agents Chemother.* 2005;49(12):4860-66.
13. Scott GM, Weinberg A, Rawlinson WD, Chou S. Multidrug resistance conferred by novel DNA polymerase mutations in human cytomegalovirus isolates. *Antimicrob Agents Chemother.* 2007;51(1):89-94.
14. Chou S, Meichsner CL. A nine-code deletion mutation in the cytomegalovirus UL97 phosphotransferase gene confers resistance to ganciclovir. *Antimicrob Agents Chemother.* 2000;44(1):183-5.
15. Kimberlin DW, Whitley RJ. Antiviral resistance: mechanisms, clinical significance, and future implications. *J Antimicrobial Chemother.* 1996;37:403-21.
16. Jabs DA, Martin BK, Ricks MO, Forman MS. Cytomegalovirus retinitis and viral resistance study group. Detection of ganciclovir resistance in patients with AIDS and cytomegalovirus retinitis: correlation of genotypic methods with viral phenotype and clinical outcome. *J Infect Dis.* 2006 Jun 15;193(12):1728-37.
17. Wolf DG, Yaniv I, Ashkenazi S, Honigman A. Emergence of multiple human cytomegalovirus ganciclovir-resistant mutants with deletions and substitutions within the UL97 gene in a patient with severe combined immunodeficiency. *Antimicrob Agents Chemother.* 2001;45(2):593-5.
18. Tchesnokov EP, Gilbert C, Boivin G, Gotte M. Role of helix P of the human cytomegalovirus DNA polymerase in resistance and hypersusceptibility to the antiviral drug foscarnet. *J Virol.* 2006;80(3):1440-50.
19. Chou S, Lurain NS, Thompson KD, Miner RC, Drew WL. Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. *J Infect Dis.* 2003 Jul 1;188(1):32-9.
20. Cherrington JM, Fuller MD, Lamy PD, et al. In vitro antiviral susceptibilities of isolates from cytomegalovirus retinitis patients receiving first- or second-line cidofovir therapy: relationship to clinical outcome. *J Infect Dis.* 1998 Dec;178(6):1821-5.
21. Jabs DA, Enger C, Forman M, Dunn JP. Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. The Cytomegalovirus Retinitis and Viral Resistance Study Group. *Antimicrob Agents Chemother.* 1998 Sep;42(9):2240-44.
22. Chou S, Lurain NS, Weinberg A, et al. 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. *Antimicrob Agents Chemother.* 1999 Jun;43(6):1500-2.
23. Mousavi-Jazi M, Schloss L, Drew WL, et al. Variations in the cytomegalovirus DNA polymerase and phosphotransferase genes in relation to foscarnet and ganciclovir sensitivity. *J Clin Virol.* 2001 Dec;23(1-2):1-15.
24. Mousavi-Jazi M, Schloss L, Wahren B, Brytting M. Point mutations induced by foscarnet (PFA) in the human cytomegalovirus DNA polymerase. *J Clin Virol.* 2003 Apr;26(3):301-6.

25. Lurain NS, Bhorade SM, Pursell KJ, et al. Analysis and characterization of antiviral drug-resistant cytomegalovirus isolates from solid organ transplant recipients. *J Infect Dis.* 2002 Sep 15;186(6):1760-8.
26. Loregian A, Appleton BA, Hogle JM, Coen DM. Residues of human cytomegalovirus DNA polymerase catalytic subunit UL54 that are necessary and sufficient for interaction with the accessory protein UL44. *J Virol.* 2004 Jan;78(1):158-167.
27. Springer KL, Chou S, Li S, et al. How evolution of mutations conferring drug resistance affects viral dynamics and clinical outcomes of cytomegalovirus-infected hematopoietic cell transplant recipients. *J Clin Microbiol.* 2005;43(1):208-13.
28. Chou S, Marousek GI, Van Wechel LC, Li S, Weinberg A. Growth and drug resistance phenotypes resulting from cytomegalovirus DNA polymerase region III mutations observed in clinical specimens. *Antimicrob Agents Chemother.* 2007 Nov;51(11):4160-62.
29. Torres-Madriz G., Boucher HW. Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients. *Clin Infect Dis.* 2008 Sep 1;47(5):702-11.
30. Chevillotte M, von Einem J, Meier BM, et al. A new tool linking human cytomegalovirus drug resistance mutations to resistance phenotypes. *Antiviral Res.* 2010 Feb;85(2):318-327.
31. Erice A, Gil-Roda C, Perez JL, et al. Antiviral susceptibilities and analysis of UL97 and DNA polymerase sequences of clinical cytomegalovirus isolates from immunocompromised patients. *J Infect Dis.* 1997 May;175(5):1087-92.
32. Picard-Jean F, Bougie I, Bisaillon M. Characterization of the DNA- and dNTP-binding activities of the human cytomegalovirus DNA polymerase catalytic subunit UL54. *Biochem J.* 2007 Nov 1;407(3):331-41.
33. Baldanti F, Lurain N, Gerna G. Clinical and biologic aspects of human cytomegalovirus resistance to antiviral drugs. *Hum Immunol.* 2004 May;65(5) 403-9.
34. Smith IL, Taskintuna I, Rahhal FM, et al. Clinical failure of CMV retinitis with intravitreal cidofovir is associated with antiviral resistance. *Arch Ophthalmol.* 1998 Feb;116(2):178-85.
35. Smith IL, Cherrington JM, Fuller MD, et al. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. *J Infect Dis.* 1997 Jul;176(1):69-77.
36. Gilbert C, and Boivin G. Human cytomegalovirus resistance to antiviral drugs. *Antimicrob Agents Chemother.* 2005 Mar;49(3):873-83.
37. Weinberg A, Jabs DA, Chou S, et al. Mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis.* 2003 Mar 1;187(5): 777-84. Epub 2003 Feb 24.
38. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. *Proc Natl Acad Sci U S A.* 2000 Jul 5;97(14):8039-44.
39. Baldanti F, Underwood MR, Talarico CL, et al. The Cys607→Tyr change in the UL97 phosphotransferase confers ganciclovir resistance to two human cytomegalovirus strains recovered from two immunocompromised patients. *Antimicrob Agents Chemother.* 1998 Feb;42(2):444-6.
40. Bestman-Smith J. Caractérisation des mutations du virus herpes simpléx impliquées dans la résistance aux antiviraux [Doctoral dissertation]. Février. 2004.
41. Wolf DG, Smith IL, Lee DJ, et al. Mutations in human cytomegalovirus UL97 gene confer clinical resistance to ganciclovir and can be detected directly in patient plasma. *J Clin Invest.* 1995 Jan;95(1):257-63.
42. Gilbert C, Handfield J, Toma E, et al. Emergence and prevalence of cytomegalovirus UL97 mutations associated with ganciclovir resistance in AIDS patients. *AIDS.* 1998 Jan 22;12(2):125-9.
43. Kuo IC, Imai Y, Shum C, et al. Genotypic analysis of cytomegalovirus retinitis poorly responsive to intravenous ganciclovir but responsive to the ganciclovir implant. *Am J Ophthalmol.* 2003 Jan;135(1):20-5.
44. Prix L, Hamprecht K, Holzhüter B, et al. Comprehensive restriction analysis of the UL97 region allows early detection of ganciclovir-resistant human cytomegalovirus in an immunocompromised child. *J Infect Dis.* 1999 Aug;180(2):491-5.
45. Boivin G, Goyette N, Gilbert C, et al. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. *J Infect Dis.* 2004 May 1 ;189(9):1615-8.
46. Erice A, Borrell N, Li W, Miller WJ, Balfour HH Jr. Ganciclovir susceptibilities and analysis of UL97 region in cytomegalovirus (CMV) isolates from bone marrow recipients with CMV disease after antiviral prophylaxis. *J Infect Dis.* 1998 Aug;178(2):531-4.
47. Chou S, Marousek G, Parenti DM, et al. Mutation in region III of the DNA polymerase gene conferring foscarnet resistance in cytomegalovirus isolates from 3 subjects receiving prolonged antiviral therapy. *J Infect Dis.* 1998 Aug;178(2):526-30.
48. Jabs DA, Martin BK, Forman MS, et al. Mutations conferring ganciclovir resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis.* 2001 Jan 15;183(2):333-7.
49. Wolf DG, Yaniv I, Honigman A, et al. Early emergence of ganciclovir-resistant human cytomegalovirus strains in children with primary combined immunodeficiency. *J Infect Dis.* 1998 Aug;178(2):535-8.
50. Boivin G, Gilbert C, Gaudreau A, et al. 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. *J Infect Dis.* 2001 Dec 15;184(12):1598-1602.

51. Chou S, Waldemer RH, Senters AE, et al. Cytomegalovirus UL97 phosphotransferase mutations that affect susceptibility to ganciclovir. *J Infect Dis.* 2002 Jan 15;185(2):162-9.
52. Seo SK, Regan A, Cihlar T, et al. Cytomegalovirus ventriculoencephalitis in a bone marrow transplant recipient receiving antiviral maintenance: clinical and molecular evidence of drug resistance. *Clin Infect Dis.* 2001 Nov 1;33(9):105-8.
53. Hu H, Jabs DA, Forman MS, et al. Comparison of cytomegalovirus (CMV) UL97 gene sequences in the blood and vitreous of patients with acquired immunodeficiency syndrome and CMV retinitis. *J Infect Dis.* 2002 Apr 1;185(7): 861-7.
54. Baldanti F, Paolucci S, Parisi A, Meroni L, Gerna G. Emergence of multiple drug-resistant human cytomegalovirus variants in 2 patients with human immunodeficiency virus infection unresponsive to highly active antiretroviral therapy. *Clin Infect Dis.* 2002 Apr 15;34(8):1146-9.
55. Fillet AM, Auray L, Alain S, et al. Natural polymorphism of cytomegalovirus DNA polymerase lies in two nonconserved regions located between domains delta-C and II and between domains III and I. *Antimicrob Agents Chemother.* 2004 May;48(5):1865-8.
56. Emery VC. Progress in understanding cytomegalovirus drug resistance. *J Clin Virol.* 2001 Jun;21(3):223-8.
57. Arens M. Clinically relevant sequence-based genotyping of HBV, HCV, CMV, and HIV. *J Clin Virol.* 2001 Aug;22(1):11-29.
58. Baldanti F, Michel D, Simoncini L, et al. Mutations in the UL97 ORF of ganciclovir-resistant clinical cytomegalovirus isolates differentially affect GCV phosphorylation as determined in a recombinant vaccinia virus system. *Antiviral Res.* 2001 Apr;54(1):59-67.
59. Ijichi O, Michel D, Mertens T, Miyata K, Eizuru Y. GCV resistance due to the mutation A594P in the cytomegalovirus protein UL97 is partially reconstituted by a second mutation at D605E. *Antiviral Res.* 2002 Feb;53(2): 135-42.
60. Faizi Khan R, Mori S, Eizuru Y, Kumura Ishii K, Minamishima Y. Genetic analysis of a ganciclovir resistant human cytomegalovirus mutant. *Antiviral Res.* 1998 Dec;40(1-2):95-103.
61. Michel D, Kramer S, Höhn S, et al. Amino acids of conserved kinase motifs of cytomegalovirus protein UL97 are essential for autophosphorylation. *J Virol.* 1999 Oct;73(10):8898-901.
62. Marschall M, Stein-Gerlach M, Freitag M, et al. Direct targeting of human cytomegalovirus protein kinase pUL97 by kinase inhibitors is a novel principle for antiviral therapy. *J Gen Virol.* 2002 May;83 (Pt 5):1013-23.
63. Chou S, Miner RC, Drew WL. A deletion mutation in region V of the cytomegalovirus DNA polymerase sequence confers multidrug resistance. *J Infect Dis.* 2000 Dec;182(6):1765-8.
64. Ducancelle A, Belloc S, Alain S, et al. Comparison of sequential cytomegalovirus isolates in a patient with lymphoma and failing antiviral therapy. *J Clin Virol.* 2004 Apr;29(4):241-7.
65. Chou S, Marousek G, Guentzel S, et al. Evolution of mutations conferring multidrug resistance during prophylaxis and therapy for cytomegalovirus disease. *J Infect Dis.* 1997 Sep;176(3):786-9.
66. Eckle T, Prix L, Jahn G, et al. Drug-resistant human cytomegalovirus infection in children after allogeneic stem cell transplantation may have different clinical outcomes. *Blood.* 2000 Nov 1;96(9):3286-9.
67. Shapira MY, Resnick IB, Chou S, et al. Artesunate as a potent antiviral agent in a patient with late drug-resistant cytomegalovirus infection after hematopoietic stem cell transplantation. *Clin Infect Dis.* 2008 May 1;46(9):1455-7.
68. Chou S, Marousek G, Li S, Weinberg A. Contrasting drug resistance phenotypes resulting from cytomegalovirus DNA polymerase mutations at the same exonuclease locus. *J Clin Virol.* 2008 Sep;43(1):107-9.
69. Marfori JE, Exner MM, Marousek GI, Chou S, Drew WL. Development of new cytomegalovirus UL97 and DNA polymerase mutations conferring drug resistance after valganciclovir therapy in allogeneic stem cell recipients. *J Clin Virol.* 2007 Feb;38(2):120-5.
70. Hamprecht K, Eckle T, Prix L, et al. Ganciclovir-resistant cytomegalovirus disease after allogeneic stem cell transplantation: pitfalls of phenotypic diagnosis by in vitro selection of an UL97 mutant strain. *J Infect Dis.* 2003 Jan 1;187(1):139-43.
71. Baldanti F, Biron KK, Gerna G. Interpreting human cytomegalovirus antiviral drug susceptibility testing: the role of mixed virus populations. *J Infect Dis.* 1998 Mar;177(3):823-4.
72. Gilbert C, Bestman-Smith J, Boivin G. Resistance of herpesviruses to antiviral drugs: clinical impacts and molecular mechanisms. *Drug Resist Updat.* 2002 Apr;5(2):88-114.
73. Lurain NS, Chou S. Antiviral drug resistance of human cytomegalovirus. *Clin Microbiol Rev.* 2010 Oct;23(4):689-712.
74. Chou S. Phenotypic diversity of cytomegalovirus DNA polymerase gene variants observed after antiviral therapy. *J Clin Virol.* 2011 Apr;50(4):287-91.
75. Chou S. Recombinant phenotyping of cytomegalovirus UL97 kinase sequence variants for ganciclovir resistance. *Antimicrob Agents Chemother.* 2010 Jun;54(6):2371-8.
76. Ducancelle A, Champier G, Alain S, et al. A novel mutation in the UL54 gene of human cytomegalovirus isolates that confers resistance to foscarnet. *Antivir Ther.* 2006;11(4):537-40.
77. Martin M, Goyette N, Ives J, Boivin G. Incidence and characterization of cytomegalovirus resistance mutations among pediatric solid organ transplant patients who received valganciclovir prophylaxis. *J Clin Virol.* 2010 Apr;47(4):321-4.

78. Cihlar T, Fuller MD, Mulato AS, Cherrington JM. A point mutation in the human cytomegalovirus DNA polymerase gene selected in vitro by cidofovir confers a slow replication phenotype in cell culture. *Virology*. 1998 Sep 1;248(2):382-93.
79. Gilbert C, Azzi A, Goyette N, et al. Recombinant phenotyping of cytomegalovirus UL54 mutations that emerged during cell passages in the presence of either ganciclovir or foscarnet. *Antimicrob Agents Chemother*. 2011 Sep;55:4019–4027.
80. Hantz S, Michel D, Fillet AM, Guignon V, Champier G, Mazon MC, et. al. Early selection of a new UL97 mutant with a severe defect of ganciclovir phosphorylation after prophylaxis and short-term ganciclovir therapy in a renal transplant recipient. *Antimicrob Agents Chemother*. 2005 Apr;49:1580-1583.
81. James SH, Price NB, Hartline CB, Lanier ER, Prichard MN. Selection and recombinant phenotyping of a novel CMX001 and cidofovir resistance mutation in human cytomegalovirus. *Antimicrob Agents Chemother*. 2013 July;57:3321-3325.
82. Drouot E, Piret J, Lebel MH, Boivin G. Characterization of multiple cytomegalovirus drug resistance mutations detected in a hematopoietic stem cell transplant recipient by recombinant phenotyping. *J Clin Microbiol*. 2014 Nov;52:4043-4046.
83. Chou S, Boivin G, Ives J, Elston R. Phenotypic evaluation of previously uncharacterized cytomegalovirus DNA polymerase sequence variants detected in valganciclovir treatment trial. *J Infect Dis*. 2014 Apr;209:1219-1226.
84. Gohring K, Hamprecht K, Gerhard J. Antiviral drug- and multidrug resistance in cytomegalovirus infected SCT patients. *Comput Struct Biotechnol J*. 13 (2015) 153-159.
85. Zhang Y, Zhao Z, Sun J, Cao G, Zhao F, Hu J, Liu L, Ji Y. A new mutation in the human cytomegalovirus UL97 gene may confer ganciclovir resistance in Chinese kidney transplant recipients. *Arch Virol* (2013) 158:247–250.
86. Bourgeois C, Sixt N, Bour JB, Pothier P. Value of a ligase chain reaction assay for detection of ganciclovir resistance-related mutation 594 in UL97 gene of human cytomegalovirus. *J Virol Methods* 67 (1997) 167–175.
87. Fischer L, Laib-Sampaio K, Jahn G, Hamprecht K, Göhring K. Generation and characterization of defined HCMV UL97- and UL54-mutants conferring drug resistance. *Antiviral Res* 2013;100:575–7.
88. Hantz S, Cotin S, Borst E, Couvreur A, Salmier A, Garrigue I, et. al. Novel DNA polymerase mutations conferring cytomegalovirus resistance: input of BAC recombinant phenotyping and 3D model. *Antiviral Res* 2013;98:130–4.
89. Chou S, Ercolani RJ, Sahoo MK, Lefterova MI, Strasfeld LM, Pinsky BA. Improved detection of emerging drug-resistant mutant cytomegalovirus subpopulations by deep sequencing. *Antimicrob Agents Chemother*. 2014 Aug;58:4697-4702.
90. Fischer L, Laib Sampaio K, Jahn G, Hamprecht K, Gohring K. Identification of newly detected, drug-related HCMV UL97 and UL54 mutations using a modified plaque reduction assay. *J Clin Virol*. 2015;69:150-5
91. Andouard D., Mazon M-C, Ligat, G., Couvreur A, Pouteil-Noble C, Cahen R, et. al. Contrasting effect of new HCMV pUL54 mutations on antiviral drug susceptibility: benefits and limits of 3D analysis. *Antiviral Res*. 2016;129:115-9
92. Fischer L, Imrich E, Laib Sampaio K, Hofmann J, Jahn G, Hamprecht K, et al. Identification of resistance associated HCMV UL97- and UL54-mutations and a UL97-polymorphism with impact on phenotypic drug resistance. *Antiviral Res*. 2016; 131:1-8.
93. Chou S, Ercolani RJ, Lanier ER. Novel cytomegalovirus UL54 DNA polymerase gene mutations selected in vitro that confer brincidofovir resistance. *Antimicrob Agents Chemother*. 2016; 60:3845-8.
94. Campos S, Ribiero J, Boutolleau D, Sousa H. Human cytomegalovirus antiviral drug resistance in hematopoietic stem cell transplantation: current state of the art. *Rev Med Virol*. 2016; 26:161-182 (Web)
95. Chou S. Approach to drug-resistant cytomegalovirus in transplant recipients. *Curr Opin Infect Dis*. 2015;28:293-299.
96. Chou S, Ercolani RJ, Marousek G, Bowlin TL. Cytomegalovirus UL97 kinase catalytic domain mutations that confer multidrug resistance. *Antimicrob Agents Chemother*. 2013; 57:3375-3379.
97. Lischka P, Michel D, and Zimmermann, H. Characterization of cytomegalovirus breakthrough events in a phase 2 prophylaxis trial of letermovir (AIC246, MK 8228). *J Infect Dis*. 2016;213:23–30. DOI: 10.1093/infdis/jiv352.
98. Goldner T, Hempel C, Ruebsamen-Schaeff H, Zimmermann H, Lischka P. Geno- and phenotypic characterization of human cytomegalovirus mutants selected in vitro after letermovir (AIC246) exposure. *Antimicrob Agents and Chemother* p. 610–613 January 2014. Volume 58 Number 1. doi:10.1128/AAC.01794-13.
99. Lischka P, Zhang D, Holder D, Zimmermann H. Impact of glycoprotein B genotype and naturally occurring ORF UL56 polymorphisms upon susceptibility of clinical Human Cytomegalovirus isolates to letermovir. *Antiviral Res* 132 (2016) 204-209.
100. Marschall M, Stamminger T, Urban A, Wildum S, Ruebsamen-Schaeff H, et.al. In vitro evaluation of the activities of the novel anticytomegalovirus compound AIC246 (letermovir) against Herpesviruses and other human pathogenic viruses. *Antimicrob Agents and Chemother* p. 1135–1137. doi:10.1128/AAC.05908-11.
101. Goldner T, Zimmermann H, Lischka P. Phenotypic characterization of two naturally occurring human cytomegalovirus sequence polymorphisms located in a distinct region of ORF UL56 known to be involved in in vitro resistance to letermovir. *Antiviral Res* 116 (2015) 48–50 <http://dx.doi.org/10.1016/j.antiviral.2015.01.006>.
102. Chou S. Rapid in vitro evolution of human cytomegalovirus UL56 mutations that confer letermovir resistance. *Antimicrob Agents Chemother*, October 2015. Volume 59 Number 10 doi:10.1128/AAC.01623-15.

103. Goldner T, Hewlett G, Ettischer N, Ruebsamen-Schaeff H, Zimmermann H, and Lischka P. The novel anticytomegalovirus compound AIC246 (letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. *J Virol* Oct. 2011, p. 10884–10893. doi:10.1128/JVI.05265-11.
104. Chou S. A third component of the human cytomegalovirus terminase complex is involved in letermovir resistance. *Antiviral Res* 148 (2017) 1–4 <http://dx.doi.org/10.1016/j.antiviral.2017.10.019>.
105. Chou S. Comparison of cytomegalovirus terminase gene mutations selected after exposure to three distinct inhibitor compounds. *Antimicrob Agents Chemother* November 2017 Volume 61 Issue 11 e01325-17.
106. Chou S. Foscarnet resistance mutations mapping to atypical domains of the cytomegalovirus DNA polymerase gene. *Antiviral Res* 138 (2017) p 57-60.
107. Chou S, Ercolani RJ, Vanarsdall AL. Differentiated levels of ganciclovir resistance conferred by mutations at codons 591 to 603 of the cytomegalovirus UL97 kinase gene. *J Clin Microbiol* July 2017 Volume 55 Issue 7. 2098–2104. <https://doi.org/10.1128/JCM.00391-17>.
108. Chou S, Satterwhite LE, Ercolani RJ. New locus of drug resistance in the human cytomegalovirus UL56 gene revealed by in vitro exposure to letermovir and ganciclovir. *Antimicrob Agents Chemother*, 2018;62:e00922-18. <https://doi.org/10.1128/AAC.00922-18>.
109. Chou S, and Bowlin TL. Cytomegalovirus UL97 mutations affecting cyclopropavir and ganciclovir susceptibility. *Antimicrob Agents Chemother*, Jan 2011, p. 382-384, Vol.55, No 1 0066-4804/11 doi:10.1128/AAC.01259-10.
110. Piret J, Goyette N, Boivin G. Drug susceptibility and replicative capacity of multidrug-resistant recombinant human cytomegalovirus harboring mutations in UL56 and UL54 genes. *Antimicrob Agents Chemother* 2017. 61:e01044-17. <https://doi.org/10.1128/AAC.01044-17>.
111. Hakkia M, and Chou S. The biology of cytomegalovirus drug resistance. *Curr Opin Infect Dis*. Dec 2011; 24 (6):605-611. doi:10.1097/QCO.0b013e32834cfb58.
112. Chou S. Advances in the genotypic diagnosis of cytomegalovirus antiviral drug resistance. *Antiviral Res* 176 (2020) 104711.
113. Wong DD, vanZuylen WJ, Hamilton ST, Steingruber M, Sonntag E, Marschall M, et. al. Patient-derived cytomegaloviruses with different ganciclovir sensitivities from UL97 mutation retain their replication efficiency and some kinase activity invitro. *Antimicrob Agents Chemother* 63:e02425-18. <https://doi.org/10.1128/AAC.02425-18>.
114. Chou S, Wub J, Song K, Bo T. Novel UL97 drug resistance mutations identified at baseline in a clinical trial of maribavir for resistant or refractory cytomegalovirus infection. *Antiviral Res* 172 (2019) 104616.
115. Houldcroft CJ, Bryant JM, Depledge DP, Margetts BK, Simmonds J, Nicolaou S et al. Detection of low frequency multi-drug resistance and novel putative maribavir resistance in immunocompromised pediatric patients with cytomegalovirus. *Front. Microbiology*. 2016. Vol 7, p. 1317. doi:10.3389/fmicb.2016.01317.
116. Chou S, Watters M, Sinha R, Kleiboeker S. Ganciclovir and maribavir susceptibility phenotypes of cytomegalovirus UL97 ATP binding region mutations detected by expanded genotypic testing. *Antiviral Research*. 2021 Jul 14;105139. doi.org/10.1016/j.antiviral.2021.105139.
117. Chou S, Marousek, G.I., 2008. Accelerated evolution of maribavir resistance in a cytomegalovirus exonuclease domain II mutant. *J. Virol*, 82, 246-253.
118. Chou S, Song, K, Wu, J, Bo, T, Crumpacker C, 2020. Drug resistance mutations and associated phenotypes detected in clinical trials of maribavir for treatment of cytomegalovirus infection. *J Infect Dis*, jiaa462.
119. Chou, S, Van Wechel, L.C., Marousek, G.I., 2007b. Cytomegalovirus UL97 kinase mutations that confer maribavir resistance. *J. Infect. Dis*. 196, 91-94.
120. Cherrier L, Nasar A, Goodlet KJ, Nailor MD, Tokman S, Chou S. Emergence of letermovir resistance in a lung transplant recipient with ganciclovir-resistant cytomegalovirus infection. *Am J Transplant*.2018;18:3060–3064. <https://doi.org/10.1111/ajt.15135>
121. Sunwen Chou 1 Opposite effects of cytomegalovirus UL54 exonuclease domain mutations on acyclovir and cidofovir susceptibility. *Antiviral Res* 2021 Nov 195:105181. doi: 10.1016/j.antiviral.2021.105181.
122. Cameron M. Douglas,1 Richard Barnard,1 Daniel Holder,2 Letermovir Resistance Analysis in a Clinical Trial of Cytomegalovirus Prophylaxis for Hematopoietic Stem Cell Transplant Recipients. *J. Infect. Dis*. 2020:221 (1 April)
123. Chou, Sunwen et al. *The Journal of Infectious Diseases*, Volume 229, Issue 2, 15 February 2024, Pages 413–421, <https://doi.org/10.1093/infdis/jiad293>