

Table 2 – Recommendations from various sources regarding genetic screening to prevent cutaneous adverse drug reactionsFelix L. Chan¹, Neil H. Shear² and Roni P. Dodiuk-Gad^{2,3,4}¹Mississauga Academy of Medicine, Faculty of Medicine, University of Toronto, Mississauga, ON, Canada²Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada³The Ruth and Bruce Rappaport Faculty of Medicine, Technion Institute of Technology, Israel⁴Department of Dermatology, Emek Medical Centre, Israel

Allele	Source	Recommendations	Ref.
ANTICONVULSANTS			
Carbamazepine			
HLA-A*31:01	Canadian Pharmacogenomics Network for Drug Safety (2014)	Genotype patients of all ancestries prior to prescribing carbamazepine. Use alternative medications if HLA-A*31:01-positive, accounting for cross-reactivities.	[1]
	Clinical Pharmacogenetics Implementation Consortium (2018)	Avoid use of carbamazepine in HLA-A*31:01-positive patients.	[2]
HLA-B*15:02	U.S. Food and Drug Administration (2007)	Genotype patients of Asian descent prior to prescribing carbamazepine. HLA-B*15:02-positive patients should not be treated with carbamazepine or anticonvulsants associated with SJS/TEN unless the expected benefit outweighs risks.	[3,4]
	Health Canada (2008)	Consider genotyping genetically at-risk patients.	[5]
	Hong Kong (2008)	Genotyping prior to prescribing carbamazepine was implemented as a system-wide mandatory policy in 2008. Carbamazepine is to be prescribed only for HLA-B*15:02-negative patients.	[6,7]
	UK Medicines and Healthcare Products Regulatory Agency (2008)	Genotype patients of Han Chinese, Hong Kong Chinese, or Thai ethnic origin prior to prescribing carbamazepine. HLA-B*15:02-positive patients should not be prescribed carbamazepine unless benefits clearly outweigh risks.	[8]
	Taiwan National Health Insurance (2010)	Since 2010, national health insurance covers expense of genotyping for HLA-B*15:02 in patients initiating carbamazepine.	[9]
	Singapore Health Sciences Authority (2013)	Genotyping prior to prescribing carbamazepine is considered the standard of care. Avoid use of carbamazepine in carriers of HLA-B*15:02. A 75% subsidy for genotype testing is provided for low-income patients.	[10,11]
	Clinical Pharmacogenetics Implementation Consortium (2014, 2018)	Avoid using carbamazepine in HLA-B*15:02-positive patients.	[2,12]
	Canadian Pharmacogenomics Network for Drug Safety (2014)	Genotype patients from ethnic populations where HLA-B*15:02 is prevalent (e.g. Chinese, Thai, Indian, Malay, Filipino, Indonesian) prior to prescribing carbamazepine. Use alternative medications if HLA-B*15:02 positive, accounting for cross-reactivities.	[1]
	Thailand (2014)	Since 2014, genotyping for HLA-B*15:02 covered under national universal healthcare system.	[13]
Oxcarbazepine			
HLA-B*15:02	Clinical Pharmacogenetics Implementation Consortium (2018)	Avoid use of oxcarbazepine in HLA-B*15:02-positive patients.	[2]
Phenytoin			
CYP2C9*3	Clinical Pharmacogenetics Implementation Consortium (2014)	Consider dose reduction and adjustment of maintenance doses of phenytoin according to therapeutic drug monitoring for CYP2C9*2 and CYP2C9*3-positive patients.	[14]
HLA-B*15:02	Singapore Health Sciences Authority (2013)	Avoid prescribing if patient is HLA-B*15:02-positive.	[10]

Allele	Source	Recommendations	Ref.
ANTIRETROVIRALS, NUCLEOSIDE ANALOG REVERSE TRANSCRIPTASE INHIBITORS			
Abacavir			
HLA-B*57:01	U.S. Food and Drug Administration (2008)	All patients should be screened for HLA-B*57:01 prior to initiating abacavir. Avoid use of abacavir in HLA-B*57:01-positive patients.	[15]
	European Medicines Agency (2009)	Genotype patients irrespective of ethnic origin prior to initiating abacavir. Avoid use of abacavir in HLA-B*57:01-positive patients.	[16]
	Clinical Pharmacogenetics Implementation Consortium (2012)	Genotype all abacavir-naïve patients before initiating abacavir. Avoid use of abacavir if patient is HLA-B*57:01-positive or has signs/symptoms of hypersensitivity.	[17]
XANTHINE OXIDASE INHIBITORS			
Allopurinol			
HLA-B*58:01	Clinical Pharmacogenetics Implementation Consortium (2012, 2016)	Avoid prescribing allopurinol to HLA-B*58:01-positive patients.	[18,19]
	2012 American College of Rheumatology Guidelines for Management of Gout (2012)	Consider genotyping subpopulations at higher risk for severe AHS (e.g. Koreans with stage 3 or worse CKD, and all Han Chinese and Thai patients) prior to prescribing allopurinol.	[20]
	Taiwan Department of Health (2012)	Genotype for HLA-B*58:01 prior to use of allopurinol.	[19]
	Singapore Health Sciences Authority (2016)	Consider genotyping patients with pre-existing risk factors for allopurinol-induced SCAR such as renal impairment.	[21]
	Hong Kong Department of Health Drug Office (2016)	Consider genotyping patients with pre-existing risk factors for allopurinol-induced SCAR such as renal impairment.	[22]

References

- Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. *Epilepsia* 2014;**55**(4):496–506.
- Phillips EJ, Sukasem C, Whirl-Carrillo M, Müller DJ, Dunnenberger HM, Chantratita W, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin. Pharmacol. Ther.* 2018;**103**(4):574–81.
- U.S. FDA. Information for Healthcare Professionals: Dangerous or Even Fatal Skin Reactions – Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics) [Internet]. 2007. p. 1–4. Available from: <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm>
- Ferrell PBJ, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* England; 2008 Oct;**9**(10):1543–6.
- Health Canada. Health Canada Endorsed Important Safety Information on TEGRETOL (carbamazepine) [Internet]. *Recalls Saf. Alerts* 2008 [cited 2018 Jan 1]. Available from: <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/14522a-eng.php>
- The Chinese University of Hong Kong. Re: Genetic testing prior to prescription of carbamazepine [Internet]. 2008. Available from: www.cuhk.edu.hk/med/paf/ups/HLA-B-1502.pdf%0A
- Chen Z, Liew D. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. *Neurology* 2014;**83**:1–8.
- UK MHRA. Carbamazepine: genetic testing recommended in some Asian populations. *Drug Saf. Updat.* 2008;**1**(9):2–4.
- Phillips EJ, Chung W, Mockenhaupt M, Roujeau J, Mallal SA, Bs MB. NIH Public Access. *J. Allergy Clin. Immunol.* 2011;**127**:60–6.
- Singapore HSA. HLA-B*1502 genotype testing: Towards safer use of carbamazepine [Internet]. 2016. Available from: http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Product_Safety_Alerts/2013/hla-b_1502_genotype.html
- Sung C. Genetically-mediated Serious Skin Rash: Singapore Health Sciences Authority Experience. *Res. Dir. Genet. Stevens-Johnson Syndr. Epidermal Necrolysis* [Internet] Bethesda, MD: NIH National Human Genome Research Institute; 2015. p. 1–20. Available from: <https://www.genome.gov/27560487/research-directions-in-genetically-mediated-stevensjohnson-syndrometoxic-epidermal-necrolysis/>
- Leckband SG, Kelsoe JR, Dunnenberger HM, Jr ALG, Tran E, Berger R, et al. Guideline Summary: Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing. [Clinical Pharmacogenetics Implementation Consortium]. *info@guideline.gov (NGC)* [Internet] 2013;(February):1–5. Available from: <http://guideline.gov/content.aspx?f=rss&id=39535>
- Chantratita W. Implementing Genomics in Clinical Practice/Healthcare: Thailand. *Res. Dir. Genet. Stevens-Johnson Syndr. Epidermal Necrolysis* [Internet] Bethesda, MD: NIH National Human Genome Research Institute; 2015. p. 1–47. Available from: <https://www.genome.gov/27560487/research-directions-in-genetically-mediated-stevensjohnson-syndrometoxic-epidermal-necrolysis/>
- Caudle KE, Rettie AE, Smith LH, Mintzer S, Lee MTM, Klein TE. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C9 and HLA-B Genotype and Phenytoin Dosing. 2014;**96**(5):1–28.
- U.S. FDA. Labels for NDA 020977 (Ziagen) [Internet]. 2018. p. 1–32. Available from: <https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm>
- European Medicines Agency. EPAR summary for the public: Ziagen (Abacavir) [Internet]. 2016 [cited 2018 Jan 1]. p. 1–3. Available from: http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/medicines/human/medicines/000252/human_med_001179.jsp%26mid%3DWC0b01ac058001d124

17. Martin MA, Klein TE, Dong BJ, Pirmohamed M, Haas DW, Kroetz DL. Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Abacavir Dosing. *Clin. Pharmacol. Ther.* 2012. p. 734–8.
18. Saito Y, Stamp LK, Caudle KE, Hershfield MS, McDonagh EM, Callaghan JT, et al. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin. Pharmacol. Ther.* 2016;**99**(1):36–7.
19. Hershfield MS, Callaghan JT, Tassaneeyakul W, Mushiroda T, Thorn CF, Klein TE, et al. Clinical pharmacogenetics implementation consortium guidelines for human leukocyte antigen-b genotype and allopurinol dosing. *Clin. Pharmacol. Ther.* 2013;**93**(2):153–8.
20. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res.* 2012;**64**(10):1431–46.
21. Singapore HSA. Allopurinol-induced serious cutaneous adverse reactions and the role of genotyping [Internet]. 2016. Available from: http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Product_Safety_Alerts/2016/allopurinol-inducedseriouscutaneousadversereactionsandtheroleofg.htm
22. Hong Kong Department of Health. Singapore: Allopurinol-induced serious cutaneous adverse reactions and the role of genotyping [Internet]. *Saf. Alerts Prod. Recalls* 2016 [cited 2018 Jan 1]. Available from: https://www.drugoffice.gov.hk/eps/news/showNews/newsTitle/pharmaceutical_trade/2016-09-22/en/26856.html