GENOMIC MEDICINE: CLINICAL PRIMER
https://doi.org/10.33591/sfp.50.1.u5

Unit No. 5

PHARMACOGENOMICS IN A NUTSHELL FOR GENERAL PRACTITIONERS

Ms Chua Hui Min, Dr Lo Ah Gi Elaine

ABSTRACT

Genetic variation may account for variations in drug responses that are unaccounted for by conventional efforts to optimise drug response. The use of pharmacogenomics (PGx) may optimise pharmacotherapy in terms of safety and efficacy and provide individualised therapeutic choices. There is established evidence and guidelines for multiple drug-gene pairs to support the clinical implementation of PGx and some examples that are pertinent to primary care are briefly described. This article also outlines the landscape of the use of PGx in Singapore and addresses the potential concerns about insurability and genetic counselling for PGx tests.

SFP2024; 50(1): 41-45

Keywords: Allele, Drug-gene pair, Genetic variant, Genotype, Pharmacogenomics

INTRODUCTION

Efforts to optimise drug response traditionally focus on adjusting for parameters like age, weight, organ function, and drug-drug interactions. However, there is still significant variation in drug response that is unaccounted for. Genetic factors may play a part in this and account for up to 20-95 percent of patient variability in drug response.[1] Genetic variations alter pharmacokinetics and pharmacodynamics of drugs by affecting drug transporters, drug-metabolising enzymes, drug targets, and the human leukocyte antigen (HLA) genes.

Pharmacogenomics (PGx) is the study of the relationship between genetic variations and how our body responds to medications.[2] Studies have found that up to 99 percent of patients carry at least one clinically actionable PGx variant.[3-6] In fact, an analysis of the UK biobank showed that nearly 24 percent of patients have been prescribed a drug for which they are predicted to have an atypical response based on genotyping results.[7] Local Singaporean data revealed that 99.7 percent (9,026/9,051) of SG10K_Health individuals carried at least one actionable pharmacogenomics variants out of 23 pharmacogenes with high confidence gene-drug associations, with a median of five variants per individuals.[8] Pharmacogenomics may be used to optimise pharmacotherapy in terms of safety and efficacy, thus providing individualised therapeutic choices.

There are currently multiple drug-gene pairs with established evidence for clinical implementation of PGx. Clinical information, including clinical guidelines and drug labels, potentially clinically actionable gene-drug associations, and genotype-phenotype relationships may be found in pharmacogenomics knowledge resources such as PharmGKB.[2] Some examples of these drug-gene pairs that are pertinent to general practitioner practice include allopurinol (HLA-B*58:01) and tramadol/codeine (CYP2D6).

ALLOPURINOL AND HLA-B*58:01

Allopurinol is a drug commonly used for the management of gout in the primary care settings. Although it is generally well tolerated, allopurinol is associated with severe cutaneous adverse reactions (SCARs), which manifests as drug hypersensitivity reactions, Stevens-Johnsons syndrome (SJS), and toxic epidermal necrolysis (TEN).[9] The presence of the HLA-B*58:01 allele has been strongly associated with allopurinol-induced SCARs.[10] Patients who are tested positive for HLA-B*58:01 are recommended to avoid initiating allopurinol and consider alternative agents.[11,12]

TRAMADOL/CODEINE AND CYP2D6

Prescriptions for tramadol and codeine for pain control are not uncommon in the primary care settings. Both drugs are metabolised by the CYP2D6 enzyme to more active metabolites. Variations in CYP2D6 genotype have been found to affect tramadol and codeine clinical efficacy and toxicity. Patients with CYP2D6 genotype corresponding to ultra-rapid metaboliser phenotype are at increased risk for toxicity; on the other hand, patients with CYP2D6 genotype corresponding to poor metaboliser phenotype are at risk of having reduced effectiveness from the drugs. Alternative painkillers are recommended to be used for the aforementioned groups of patients.[12,13]

LANDSCAPE OF THE USE OF PGX IN SINGAPORE

The use of PGx in optimising drug use is not new in Singapore. In April 2013, the Ministry of Health (MOH) announced that genotyping for the HLA-B*15:02 allele prior to initiating carbamazepine therapy in new patients of Asian ancestry is considered the standard of care in Singapore.[14] Carbamazepine was associated with approximately 20

MS CHUA HUI MIN
Senior Clinical Pharmacist
Department of Pharmacy, National University Hospital

DR LO AH GI ELAINE
Principal Clinical Pharmacist
Department of Pharmacy, National University Hospital

percent (24 out of 111) of the SJS cases reported to the Health Science Authority (HSA) of Singapore from January 1997 to May 2004 and was listed as the only suspected causative agent in two-thirds of the reports. Local studies showed that there is a strong association between the HLA-B*15:02 allele and carbamazepine-induced SJS/TEN, and testing for the allele is cost-effective.[15,16] This regulatory recommendation, alongside a 75 percent subsidy for HLA-B*15:02 genotyping to all subsidised patients at public healthcare institutions, have contributed to a 92 percent reduction in cases of SJS/TEN that are associated with carbamazepine within five years.[17]

The Health Science Authority of Singapore (HSA) and MOH have also issued a communication in March 2016 to inform that HLA-B*58:01 genotyping prior to the initiation of allopurinol is not required as standard of care. This recommendation was made in view of the low positive predictive value of 2 percent and lack of cost-effective alternatives for urate-lowering therapies.[18] Subsequently, HSA issued a reminder in 2021 to advise healthcare professionals to consider HLA-B*58:01 genotyping in patients starting on allopurinol who have other pre-existing risk factors for allopurinol-induced SCAR – such as renal impairment and advanced age – in order to identify patients who are at a greater risk.[19]

PGx recommendations can also be found in local clinical guidelines. The National HIV Programme for Singapore recommends considering HLA-B*57:01 testing prior to the use of abacavir in non-Chinese patients, including Indian and Malay patients with late-stage HIV infection (CD4 <200 cells/mm^3) on a patient-to-patient basis.[20] The Asia-Pacific Working Group on Inflammatory Bowel Disease stated that while routine TPMT testing prior to thiopurine (e.g., azathioprine) initiation is not recommended in Asian population, NUDT15 genotyping is recommended if available.[21]

Since 2017, Singapore has embarked on a National Precision Medicine (NPM) Strategy. This 10-year national precision medicine research roadmap aims to enhance and accelerate biomedical research, health outcomes, and economic growth.[22] Precision Health Research, Singapore (PRECISE) is a central entity set up to coordinate a whole-of-government effort to implement Phase II of the NPM strategy. Clinical Implementation of Pre-emptive Pharmacogenomic Testing as a Precision Medicine Tool in Routine Clinical Practice in Singapore is one of five Clinical Implementation Pilots awarded under PRECISE to study the cost-effectiveness and implementation barriers of incorporating pre-emptive multi-drug/multi-gene PGx testing as a precision medicine clinical tool in routine clinical practice. Results from the PGx panel testing and recommendations for drugs in the panel will be accessible to patients on a digital platform in collaboration with a local startup. This will enable the sharing of PGx information with clinicians from different institutions, including General Practitioners (refer to **Figure I**).

CONCERNS ABOUT INSURABILITY AND GENETIC COUNSELLING

Physicians in primary care may encounter patients with concerns about insurability when pharmacogenomics tests are offered. Pharmacogenomics tests are considered as predictive genetic tests and are covered under the "Moratorium on Genetic Testing and Insurance" developed by MOH and the Life Insurance Association (LIA).[23] An insurer is not allowed to request the disclosure of and/or use predictive genetic test results to underwrite five products (life, total permanent disability, long-term care, critical illness, and disability income insurances) unless both the sum assured exceeds the financial limits specified in the Moratorium and the applicant has taken a predictive genetic test from the list of approved predictive genetic tests specified in the Moratorium (i.e., BRCA1, BRCA2, and Huntington's disease). The insurer is also not allowed to require or pressure (directly or indirectly) the individual to undertake a genetic test for the purpose of insurance application, even if the individual has a family history of genetic condition(s). This information can be used to assure individuals undergoing pharmacogenomics testing that it is unlikely to affect their insurability.

Physicians may be concerned whether genetic counselling is required for PGx testing. Genetic counselling refers to the process of advising individuals and families affected by or at risk of genetic disorders to help them understand and adapt to the medical, psychological, and familial implications of genetic contributions to specific health conditions. In answering this question, physicians may refer to the MOH Circular issued in December 2020 titled "Updates to Code of Practice on the Standards for the Provision of Clinical Genetic/Genomic Testing Services and Clinical Laboratory Genetic/Genomic Testing Services".[24] The Code of Practice stratifies genetic tests into three levels. The majority of the PGx tests fall under Level 1 (as specified in Annex B of **Table I**) – where 1) the tests are deemed to be likely appropriately ordered and correctly interpreted by most registered medical practitioners; 2) most medical practitioners are likely to be able to appropriately explain the test results to the patients; and 3) most registered medical practitioners are likely to be able to implement the appropriate referrals, investigations and/or follow-up plans based on the test results. For Level 1 genetic tests, while pre-test and post-test genetic counselling is not applicable, pre/post-test counselling as per other diagnostic procedures is advised.

CONCLUSION

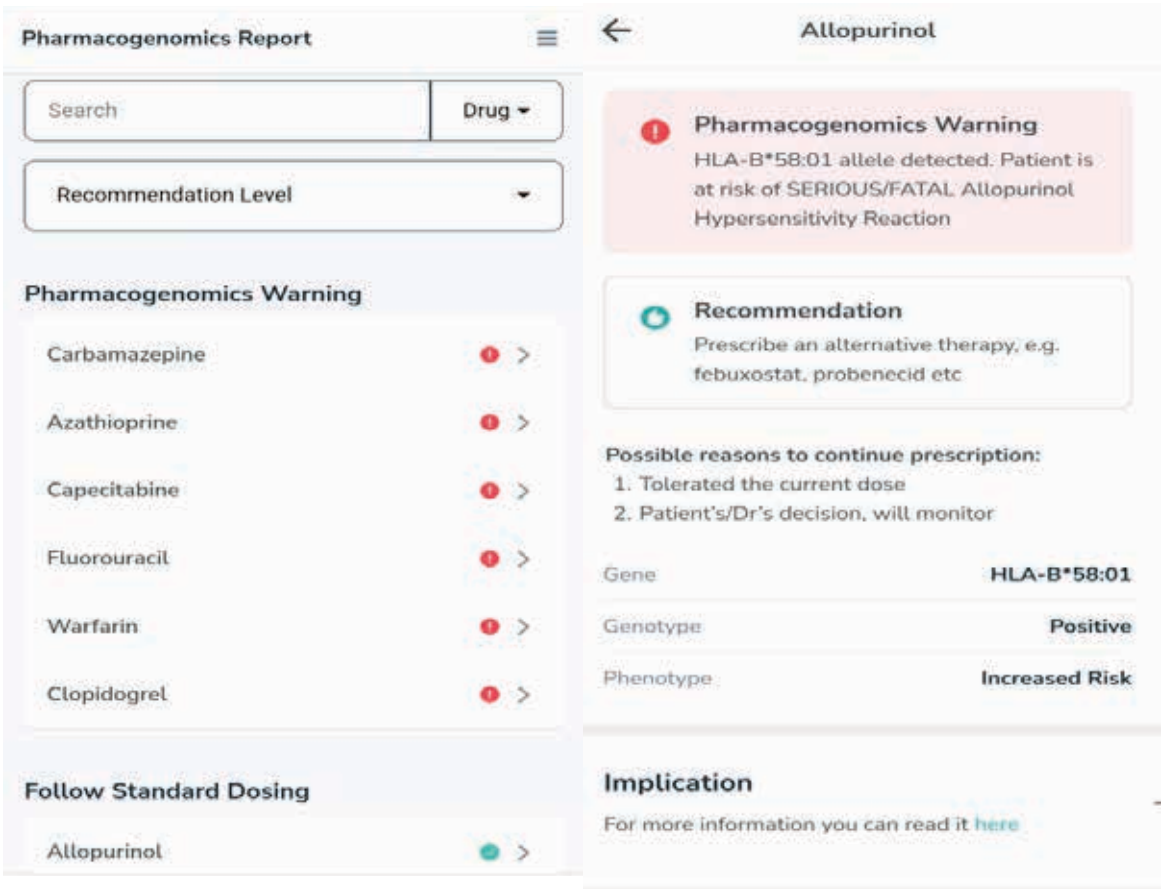
There is established evidence and guidelines for multiple drug-gene pairs to support clinical implementation of PGx, which can potentially optimise drug response and provide individualised therapeutic choices. These include drugs commonly prescribed in the primary setting. Under the "Moratorium on Genetic Testing and Insurance", pharmacogenomics tests are considered as predictive genetic tests and are unlikely to affect the insurability of the

individuals taking such tests. Most PGx tests fall under Level 1 genetic tests, where genetic counselling is not mandatory.

REFERENCES

1. Belle DJ, Singh H. Genetic factors in drug metabolism. Am Fam physician. 2008 Jun 1;77(11):1553-60. PMID: 18581835.
2. Whirl-Carrillo M, Huddart R, Gong L, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther. 2021 Sep;110(3):563-572. doi: 10.1002/cpt.2350. Epub 2021 Jul 22. PMID: 34216021; PMCID: PMC8457105.
3. Dunnenberger HM, Crews KR, Hoffman JM, et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. Annu Rev Pharmacol Toxicol. 2015;55:89-106. doi: 10.1146/annurev-pharmtox-010814-124835. Epub 2014 Oct 2. PMID: 25292429; PMCID: PMC4607278.
4. Chanfreau-Coffinier C, Hull LE, Lynch JA, et al. Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users. JAMA Netw Open. 2019 Jun 5;2(6):e195345. doi: 10.1001/jamanetworkopen.2019.5345. PMID: 31173123; PMCID: PMC6563578.
5. Wang L, Scherer SE, Bielinski SJ, et al. Implementation of preemptive DNA sequence-based pharmacogenomics testing across a large academic medical center: The Mayo-Baylor RIGHT 10K Study. Genet Med. 2022 May;24(5):1062-1072. doi: 10.1016/j.gim.2022.01.022. Epub 2022 Mar 21. PMID: 35331649; PMCID: PMC9272414.
6. Bush WS, Crosslin DR, Owusu-Obeng A, et al. Genetic variation among 82 pharmacogenes: The PGRNseq data from the eMERGE network. Clin Pharmacol Ther. 2016 Aug;100(2):160-9. doi: 10.1002/cpt.350. Epub 2016 Jun 1. PMID: 26857349; PMCID: PMC5010878.
7. McInnes G, Lavertu A, Sangkuhl K, Klein TE, Whirl-Carrillo M, Altman RB. Pharmacogenetics at scale: an analysis of the UK Biobank. Clin Pharmacol Ther. 2021 Jun;109(6):1528-1537. doi: 10.1002/cpt.2122. Epub 2020 Dec 17. PMID: 33237584; PMCID: PMC8144239.
8. Chan SH, Bylstra Y, Teo JX, et al. Analysis of clinically relevant variants from ancestrally diverse Asian genomes. Nat Commun. 2022 Nov 5;13(1):6694. doi: 10.1038/s41467-022-34116-9. PMID: 36335097; PMCID: PMC9637116.
9. Halevy S, Ghislain PD, Mockenhaupt M, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008 Jan;58(1):25-32. doi: 10.1016/j.jaad.2007.08.036. Epub 2007 Oct 24. PMID: 17919772.
10. Saito Y, Stamp LK, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther. 2016 Jan;99(1):36-7. doi: 10.1002/cpt.161. Epub 2015 Jul 16. PMID: 26094938; PMCID: PMC4675696.
11. Manson LE, Swen JJ, Guchelaar HJ. Diagnostic Test Criteria for HLA Genotyping to Prevent Drug Hypersensitivity Reactions: A Systematic Review of Actionable HLA Recommendations in CPIC and DPWG Guidelines. Front Pharmacol. 2020 Sep 23;11:567048. doi: 10.3389/fphar.2020.567048. PMID: 33071783; PMCID: PMC7538700.
12. Dutch Pharmacogenetics Working Group. KNMP Knowledge Base: Knowledge Document Pharmacogenetics. Netherland: Dutch Pharmacogenetics Working Group; [updated: 2022; accessed: 108/10/2023]. Available from: https://www.knmp.nl/media/105
13. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021 Oct;110(4):888-896. doi: 10.1002/cpt.2149. Epub 2021 Feb 9. PMID: 33387367; PMCID: PMC8249478.
14. Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients. Singapore: Health Sciences Authority; 2013 [updated: 29 Aug 2013; accessed: 18 Oct 2023]. Available from: https://www.hsa.gov.sg/announcements/safety-alert/recommendations-for-hla-b-1502-genotype-testing-prior-to-initiation-of-carbamazepine-in-new-patients (hsa.gov.sg)
15. Toh DS, Tan LL, Aw DC, et al. Building pharmacogenetics into a pharmacovigilance program in Singapore: using serious skin rash as a pilot study. Pharmacogenomics J. 2014 Aug;14(4):316-21. doi: 10.1038/tpj.2013.46. Epub 2014 Jan 7. PMID: 24394201.
16. Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B* 1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology. 2012 Sep 18;79(12):1259-67. doi: 10.1212/WNL.0b013e31826aac73. Epub 2012 Sep 5. PMID: 22955130.
17. Sung C, Tan L, Limenta M, Ganesan G, Toh D, Chan CL. Usage Pattern of Carbamazepine and Associated Severe Cutaneous Adverse Reactions in Singapore Following Implementation of HLA-B*15:02 Genotyping as Standard-of-Care. Front Pharmacol. 2020 May 7;11:527. doi: 10.3389/fphar.2020.00527. PMID: 32457602; PMCID: PMC7221117.
18. Role of HLA-B*5801 genotyping prior to initiation of allopurinol. Singapore: Health Sciences Authority; 2016 [updated: 23 Mar 2016; accessed: 18 Oct 2023]. Available from: https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/role-of-hla-b-5801-genotyping-prior-to-initiation-of-allopurinol
19. Allopurinol-induced severe cutaneous adverse reactions and the role of HLA-B*5801 genotyping – a reminder. Singapore: Health Sciences Authority; 2021 [updated: 21 Dec 2021; accessed: 18 Oct 2023]. Available from: https://www.hsa.gov.sg/announcements/safety-alert/allopurinol-induced-severe-cutaneous-adverse-reactions-and-the-role-of-hla-b-5801-genotyping-a-reminder
20. Choy CY, Wong CS, Kumar PA, et al. Recommendations for the use of antiretroviral therapy in adults living with HIV in Singapore. Singapore Med J. 2022 Apr 3. doi: 10.11622/smedj.2021174. Epub ahead of print. PMID: 35366662.
21. Ooi CJ, Hilmi I, Banerjee R, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. J Gastroenterol Hepatol. 2019 Aug;34(8):1296-1315. doi: 10.1111/jgh.14648. Epub 2019 Jul 1. PMID: 30848854.
22. Wong E, Bertin N, Hebrard M, et al. The Singapore National Precision Medicine Strategy. Nat Genet. 2023 Feb;55(2):178-186. doi: 10.1038/s41588-022-01274-x. Epub 2023 Jan 19. PMID: 36658435.
23. Moratorium on Genetic Testing and Insurance. Singapore: Ministry of Health; 2021 [updated: 6 Jun 2022; accessed: 18 Oct 2023]. Available from: https://www.moh.gov.sg/resources-statistics/moratorium-on-genetic-testing-and-insurance
24. Regulations, Guidelines and Circulars. Singapore: Ministry of Health; 2021 [updated: 7 Nov 2022; accessed: 18 Oct 2023]. Available from: https://www.moh.gov.sg/licensing-and-regulation/regulations-guidelines-and-circulars/details/updates-to-code-of-practice-on-the-standards-for-the-provision-of-clinical-genetic-genomic-testing-services-and-clinical-laboratory-genetic-genomic-testing-services

Figure I. Pharmacogenomics Report on Digital Platform



Permission to share screenshots obtained from Nalagenetics®

Table I. Pharmacogenomics Tests classified as Level I Genetic Tests[23]

Gene(s)/Variant(s) Tested	Examples of indications for which gene(s)/ variant(s) are tested	Examples of drugs that gene(s)/ variant(s) are tested to inform
VKORC1, CYP4F2, and CYP2C9	Thromboembolic/excessive clotting disorder Anticoagulation	Warfarin
TPMT, *NUDT15*	Autoimmune disorder Inflammatory disorder Cancer	Thiopurines (azathioprine, mercaptopurine, and thioguanine)
UGT1A1	Cancer	Irinotecan
*HLA-B*5701*	HIV	Abacavir
*HLA-B*5801*	Gout, hyperuricemia	Allopurinol
*HLA-B*1502*	Epilepsy	Carbamazepine, phenytoin
HLA-B27	Juvenile Arthritis (ERA)/autoimmune disorder/allergy	Sulphasalazine
CYP3A5	Need for immunosuppression, e.g., post-transplant	Tacrolimus

CYP2C19	Major depressive and anxiety disorders	Citalopram, Escitalopram
	Coronary heart disease	Clopidogrel
	Invasive fungal infections	Voriconazole
CYP2C19 and CYP2D6	Major depressive disorders	Amitriptyline
CYP2D6	Major depressive and anxiety disorders	Fluvoxamine, Paroxetine, Nortriptyline
	Pain management	Codeine, Tramadol, Oxycodone
	Suppression of nausea and vomiting	Ondansetron, Tropisetron
	Cancer	Tamoxifen
*CYP2C9, HLA-B*1502*	Epilepsy	Phenytoin
SLCO1B1	Lipid lowering	Simvastatin
Actionable PGx Genotyping Panel *(CYP3A5, CYP2C9, CYP2C19, CYP2D6, CYP4F2, NUDT15, TPMT, VKORC1, SLCO1B1, HLA-B*1502, HLA-B*5701, HLA-B*5801)*	Pre-emptive genotyping that provides an assessment for genes with strong drug gene associations	Multiple
DPYD	Cancer	5-fluorouracil chemotherapy

LEARNING POINTS

- **Genetic variations help to explain up to 20 to 95 percent of variation in drug response. Pharmacogenomics (PGx) is the study of the relationship between genetic variations and how our body responds to medications.**
- **Clinical guidelines are available to guide individualised therapeutic choices based on pharmacogenomics test results.**
- **Examples of drug-gene interactions that are commonly observed in the primary care setting include allopurinol-HLA-B*58:01, tramadol-CYP2D6, and simvastatin-SLCO1B1.**
- **Pharmacogenomics tests are considered predictive genetic tests and are unlikely to affect the insurability of patients.**
- **Most PGx tests fall under Level 1 genetic tests, where genetic counselling is not mandatory.**