

Pharmacogenomics in psychiatry: Practice recommendations from an Asian perspective (2024)

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ABSTRACT

Introduction: Pharmacogenomic testing in psychiatry is an emerging area with potential clinical application of guiding medication choice and dosing. Interest has been fanned by commercial pharmacogenomic providers who have commonly marketed combinatorial panels that are direct-to-consumer. However, this has not been adopted widely due to a combination of barriers that include a varying evidence base, clinician and patient familiarity and acceptance, uncertainty about cost-effectiveness, and regulatory requirements. This review aims to examine recent updates in this field and provide a contextualised summary and recommendations for Asian populations in order to guide healthcare professionals in psychiatric practice.

Method: A review of recent literature about current evidence and guidelines surrounding pharmacogenomics in psychiatric practice was carried out with particular attention paid to literature evaluating Asian populations. The Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework was applied. Consensus meetings comprising workgroup psychiatrists from the public and private sectors were held prior to arriving at the key recommendations.

Results: Pharmacogenomic testing should be mainly limited to drug-gene pairs with established clinical evidence, such as antidepressants and CYP2C19/CYP2D6. Direct-to-consumer pharmacogenomic panels that assay multiple genes and analyse them via proprietary algorithms, are not presently recommended in Singapore's psychiatric setting due to inconclusive evidence on clinical outcomes.

Conclusion: Pharmacogenomic testing in psychiatry is not recommended as standard clinical practice. Exceptions may include concerns about drug concentrations or potential severe adverse drug reactions. Studies investigating newly identified drug-gene associations, and clinical effectiveness and cost-

effectiveness of utilising pharmacogenomic testing in psychiatry is encouraged.

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Keywords: genetics, mental health, pharmacogenomics, pharmacology, psychiatry

CLINICAL IMPACT

What is New

- This article provides an update on the developments in pharmacogenomic testing in psychiatry and its current position in Singapore's landscape.
- Pharmacogenomic testing should be mainly limited to drug-gene pairs with established clinical evidence, such as antidepressants and CYP2C19/CYP2D6.
- Direct-to-consumer pharmacogenomic panels that assay multiple genes and analyse them via proprietary algorithms, are not presently recommended in Singapore's psychiatric setting due to inconclusive evidence on clinical outcomes.

Clinical Implications

- The practice recommendations can guide healthcare professionals on the utilisation of pharmacogenomic testing in psychiatric practice, particularly as an augmenting tool to guide medication selection and dosing, and limited to the known drug-gene pairs with established clinical evidence.

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INTRODUCTION

Pharmacogenomic testing in psychiatry is an emerging area with the potential clinical application of guiding medication choice and dosing. Interest in this area has been fanned by commercial pharmacogenomic providers, who have commonly marketed multiple-gene or combinatorial panels that are direct-to-consumer tests. However, this has not been adopted widely due to a combination of barriers that include a varying evidence base, clinician and patient familiarity and acceptance, uncertainty about cost-effectiveness, and regulatory requirements. This was highlighted in a survey of clinicians engaged in the practice of psychiatry in Singapore and pharmacists from Singapore's Institute of Mental Health conducted by Chan et al.¹ Only 46.4% of respondents felt they were competent to order pharmacogenomic tests in psychiatry, with cost-effectiveness and the lack of clear guidelines raised as possible barriers to clinical implementation.

This review aimed to examine recent updates in pharmacogenomic testing in psychiatry, and provide a contextualised summary and recommendations for Singapore and the wider Asian audience. The recommendations serve to guide healthcare professionals on the utility of pharmacogenomic testing in psychiatric practice.

Singapore updates and practices

The first Standards for the Provision of Clinical Genetic/Genomic Testing Services and Clinical Laboratory Genetic/Genomic Testing Services were issued as a Code of Practice (COP) by Singapore's Ministry of Health (MOH) on 1 July 2018. In a further circular dated 16 December 2020,² MOH shared an updated COP following feedback from stakeholders and consultation with the Genetic Testing Advisory Committee.

The pertinent change for the field of psychiatry was that tests for certain genes/variants were approved for classification as Level 1 genetic tests by the Director of Medical Service (Annex B).² In particular, tests for *CYP2C19*, *CYP2D6* and "Actionable Pharmacogenomic Genotyping Panel" have been classified as Level 1 genetic tests. The effect of this change is that these tests can now be ordered by most registered medical practitioners, as compared to previously when they were deemed as Level 2 genetic tests, which required the registered medical practitioner to meet additional requirements, such as having relevant qualification or training in clinical genetics with at least 2 years of relevant working experience.

MOH had also published a guidance document³ for the provision of non-clinical genetic testing

in May 2021. It provides a definition of what constitutes clinical genetic testing, wherein any test that predicts a person's drug response has been included in the scope. The document also emphasised that any genetic testing that performs the same function as clinical genetic testing would be considered clinical, regardless of any disclaimers used. Together with the COP, it is stipulated that clinical genetic testing services can only be provided to consumers by healthcare institutions licensed under the Private Hospitals and Medical Clinics Act. In other words, clinical genetic tests cannot be offered as direct-to-consumer tests in Singapore. However, it is also crucial to note that MOH's regulatory framework does not apply to overseas providers, hence the need for practitioners to stay abreast of current evidence and the range of available services.

In the current Singapore psychiatric practice, as shared by members of our workgroup, pharmacogenomic testing has usually been employed to address either of the 2 following clinical issues: for aiding medication selection and dosing, and for avoiding severe adverse reactions with psychotropics. For the former, the patient commonly presents with a history of treatment resistance and failing multiple previous medication trials. With the aid of pharmacogenomic gene testing, the metaboliser status (or how quickly the body processes the drug) can be established, which helps in guiding future medication choice and dose-finding. As for the latter, psychiatrists would test for immunologic genes such as *HLA-B*1502* before prescribing carbamazepine to reduce the risk of potentially rare but severe adverse effects that may arise. This practice is standard of care and genotyping for the *HLA-B*1502* allele is subsidised by MOH.

The financial cost of pharmacogenomic tests is not insignificant and should be taken into consideration when utilised, with single gene testing costing around SGD100–200⁴ and combinatorial panels costing upwards of SGD400⁵ as of time of publishing.

METHOD

The consensus workgroup comprised psychiatrists from both the public and private sector. The workgroup evaluated the available literature up till June 2023 through a search of PubMed, Embase and CENTRAL databases. Keywords searched included "pharmacogenetic", "pharmacogenomic", "psychiatry" and "psychiatric disorders". The literature assessed included guidelines, meta-analyses, systematic reviews and randomised controlled trials (RCTs) in the English language. For RCTs, the search was limited from 2019 to

evaluate recent evidence reflecting the advancements in pharmacogenomic testing. The workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision framework⁶ to evaluate the available evidence and arrive at the recommendations. Regular meetings were held, with workgroup members discussing each recommendation and arriving at a consensus when all members agreed. The workgroup adopted the Reporting Items for Practice Guidelines in Healthcare (RIGHT) checklist⁷ in setting out the guideline.

RESULTS

Available evidence and guidelines

The majority of pharmacogenomics evidence in psychiatry revolves around antidepressants. Most studies have evaluated the pharmacogenomic variants, in particular the cytochrome *P450* (*CYP450*) enzymes *CYP2C19* and *CYP2D6*. However, there exists discordance between pharmacogenomic resources such as the US Food and Drug Authority (FDA) drug labels and guidelines issued by the Clinical Pharmacogenetic Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) stemming from differences in approaches and access to

information.^{8,9} These resources are subject to reviews and updates and should be checked periodically in view of anticipated advancements in the field. In 2018, the FDA had initially released a safety communication¹⁰ warning that despite the potential of pharmacogenomic testing, pending further scientific study, pharmacogenomic testing should not be used to provide information on a person’s ability to respond to any specific medication to treat conditions such as depression, heart conditions, acid reflux and others. The FDA provided a further update to this in 2020, announcing a collaborative review of scientific evidence to support associations between genetic information and specific medications. The updated stance was accompanied by the publication of a Table of Pharmacogenetic Associations¹¹ which the FDA had deemed that while there was sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants may experience differential therapeutic effects or risks of adverse events, most of the listed associations had not been evaluated in terms of clinical outcomes—such as improved therapeutic effectiveness or increased risk of specific adverse events—and that the FDA was not necessarily advocating use of a pharmacogenetic test before prescribing the corresponding medication.

Table 1. Antidepressants with actionable pharmacogenomic guidelines (CPIC and DPWG).

Antidepressant	CPIC	DPWG
Sertraline	CYP2C19, CYP2B6	CYP2C19
Citalopram	CYP2C19	CYP2C19
Escitalopram	CYP2C19	CYP2C19
Amitriptyline	CYP2C19, CYP2D6	CYP2D6
Clomipramine	CYP2C19, CYP2D6	CYP2D6
Doxepin	CYP2C19, CYP2D6	CYP2D6
Trimipramine	CYP2C19, CYP2D6	-
Imipramine	CYP2C19, CYP2D6	CYP2C19, CYP2D6
Paroxetine	CYP2D6	CYP2D6
Fluvoxamine	CYP2D6	-
Venlafaxine	CYP2D6	CYP2D6
Vortioxetine	CYP2D6	-
Nortriptyline	CYP2D6	CYP2D6
Desipramine	CYP2D6	-

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group

The CPIC^{12,13} and DPWG¹⁴ guidelines both carry recommendations for dose adjustments for certain antidepressants based on *CYP2C19* and *CYP2D6* phenotypes (Table 1). Additionally, the CPIC guideline carries a recommendation for initial dose adjustment in poor metabolisers of *CYP2B6*¹² and sertraline. Some of the notable antidepressants in the local context that currently do not have actionable pharmacogenomic guidelines include agomelatine, bupropion, fluoxetine, mirtazapine and trazodone.

As for antipsychotics, most studies to date have focused primarily on *CYP2D6*, with aripiprazole and risperidone most researched. Only the DPWG carries actionable guidelines¹⁵ for 6 antipsychotics metabolised by *CYP2D6*, namely, aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for *CYP3A4* poor metabolisers and quetiapine. No therapy adjustments are recommended for drug-gene pairs of *CYP2D6* and clozapine, flupentixol, olanzapine or quetiapine, and also not for *CYP1A2* and clozapine or olanzapine.

Regarding attention-deficit/hyperactivity disorder (ADHD) medications, current available evidence supports the optimisation of atomoxetine dosing based on variation in *CYP2D6*.^{16,17} Poor metabolisers of atomoxetine are more likely to achieve the necessary blood concentrations for clinical effectiveness. DPWG recommends starting with the normal initial dose for poor metabolisers and being vigilant for side effects with a view to reducing the dose of atomoxetine in this group.¹⁷ Likewise, CPIC recommends initiating with a standard starting dose and adjusting based on clinical response and metaboliser phenotype.¹⁶

There is limited or inconsistent evidence linking pharmacokinetic variants and treatment outcomes for most other common, notable psychotropic classes, such as mood stabilisers and anxiolytics. For the commonly employed mood stabilisers and anticonvulsants, valproate has no actionable guidelines for pharmacokinetic gene variants, while lithium and pregabalin are not hepatically metabolised and are excreted unchanged renally. As for the anxiolytics, the FDA Table of Pharmacogenetic Associations lists 2 benzodiazepines currently, namely, clobazam with *CYP2C19* (where data supports therapeutic management recommendations) and diazepam with *CYP2C19* (with potential impact on pharmacokinetic properties only).

Particular attention has to be paid to the immunologic genes *HLA-A* and *HLA-B* due to the potential for rare but severe side effects, such as Stevens-Johnson syndrome and toxic epidermal

necrolysis following exposure to certain mood stabilisers such as carbamazepine. This is especially relevant in Singapore's context as the *HLA-B*1502* allele is more prevalent in Asian ethnicities with an estimated population frequency of 14.87%.¹⁸ It remains that *HLA-B*1502* genotyping before prescribing carbamazepine is the only mandated pharmacogenomic test for psychiatry in Singapore.

The International Society of Psychiatric Genetics conducted a review and summarised the available evidence and treatment guidelines relating to pharmacogenomic testing in psychiatry.¹⁹ They concluded that pharmacogenomic testing should be viewed as a decision-support tool for enhancing, rather than an alternative to standard treatment protocols. At the time of the published review, the available evidence and prescribing guidelines supported the use of pharmacogenomic testing to guide medication selection and dosing in several clinical contexts, particularly for antidepressants (*CYP2C19* and *CYP2D6*), antipsychotics (*CYP2D6*), anticonvulsants (*CYP2C19*, *HLA-A* and *HLA-B*) and the ADHD medication atomoxetine (*CYP2D6*), whereas current evidence did not support the testing of pharmacodynamic genes (e.g. *SLC6A4*, *COMT*, *MTHFR*) to inform prescribing of psychiatric medication. Additionally, a recommendation was included to screen for variants in *POLG* in patients suspected of having a mitochondrial disorder, and for *OTC* and *CPS1* in those suspected of having a urea cycle disorder prior to initiation of valproate, as the use of valproate in those with such disorders and particular gene variants may risk inducing liver toxicity, hyperammonaemia and encephalopathy.²⁰

The Dutch Clinical Psychiatric Association also published their first guideline²¹ on the use of pharmacogenetics in clinical psychiatric practice in 2021. Their general recommendations include considering genotyping when there is an indication (e.g. side effects or inefficacy), utilising genotype information if already available at the time of prescription, and involving patients in shared decision-making. At the time of publication, pre-emptive genotyping was not yet recommended for psychotropic drugs.

Combinatorial panels

Pharmacogenomic tests may either evaluate a single gene or multiple genes, with the latter termed “combinatorial” panels or approaches. Some combinatorial panels are produced by commercial providers, adopting a direct-to-consumer model, i.e. without healthcare professional input. Providers of these commercial panels often aggregate and analyse information from several genes using proprietary algorithms to provide recommenda-

tions for treatment choices. Pre-emptive panels that genotype for multiple genes with actionable variants (upon which clinicians can consider in their prescribing decisions) are also under development and investigation for clinical utility.^{22,23}

A review of recent combinatorial pharmacogenomics testing studies revealed inconclusive or negative findings. The GAPP-MDD randomised-controlled trial (RCT) in Canada by Tiwari et al.,²⁴ which evaluated the GeneSight® Psychotropic combinatorial pharmacogenomic testing, found that there was no statistically significant difference between the guided-care group and the treatment-as-usual (TAU) group in response and remission rates after 8 weeks. The GUIDED trial²⁵ which also employed the GeneSight® Psychotropic test, found in their per-protocol analysis that at week 8, there was no significant difference in symptom improvement between the guided-care and TAU groups. However, there were statistically significant improvements in response and remission at week 8 for the guided-care group.

The PRIME Care open-label, randomised trial,²⁶ which likewise employed the GeneSight® panel, found that while the prescription of medications with predicted drug-gene interactions was significantly reduced in the intervention group compared to the TAU group, there was no significant difference in the remission and response rates at week 24 between groups in the treatment of depression. The PRIME Care group also noted that many of the subjects had no or only moderate predicted drug-gene interactions, which would have provided no relevant clinical information in medication choice and no effect on depression outcomes. Perlis et al.²⁷ conducted a double-blinded RCT using the Genecept Assay and found that there was no significant difference between the guided-care and TAU groups at week 8. Shan et al.²⁸ employed a proprietary assay (Conlight Medical Institute) in their 8-week, single-centre, rater-blinded study of 71 subjects of Han Chinese ethnicity. At the end of 8 weeks, there were no significant differences found in response and remission rates between the guided-care and TAU groups.

Aside from the inconclusive findings of the combinatorial approaches thus far, one of the main challenges to their adoption includes the variability across tests and the lack of regulatory standards. Selection of genes for inclusion in the assays varies by provider; and often, genes with insufficient evidence to guide prescribing are included. Even within the same selected genes, variations in the selected polymorphisms appear across the different tests, adding a layer of complexity in comparing and aggregating studies. The

proprietary algorithms developed by each test provider to weigh the influence of each individual genotype in guiding medication selection lacks transparency, lends to the difficulty in generalising or aggregating results and can carry the risk that an individual alters their medication dosage so that their condition worsens. Most of the above studies also highlighted, as a limitation to generalisability of their studies, the majority Caucasian make-up of their cohorts and this is pertinent to practices that mainly interact with Asian populations.

Asian perspective

The majority of available literature on pharmacogenomics in psychiatry have chiefly examined populations of European ancestry and there is a gap in existing literature evaluating Asian populations. Ethnic variations in genetic polymorphisms are established and may result in different metaboliser phenotypes.^{29,30} For the most studied group of CYP450 enzymes, the activity of CYP2C19 and CYP2D6 have been found to be lower in Asians compared to Caucasians.^{29,31} An implication of this can be seen in the relationship between CYP2C19 and treatment response to escitalopram in panic disorder. He et al.³² reported that in Chinese patients who were poor metabolisers, there was a higher treatment response compared to the extensive metabolisers. Few studies have evaluated clinical outcomes of pharmacogenomic testing in Asian populations and this is an area that should be encouraged. Apart from the aforementioned Shan et al.²⁸ study, Han et al. (corrigendum published in 2020)³³ evaluated the Neuropharmgen® assay in 100 Korean patients with depression. Both the guided and TAU arms had substantial improvements in terms of total Hamilton Depression Rating Scale (Ham-D) scores at the end of 8 weeks, with the guided arm having a significantly greater reduction in Ham-D, increased response rate but no significantly different remission rate compared to the TAU arm.

As for the immunologic genes *HLA-A* and *HLA-B*, a meta-analysis conducted by Deng et al.³⁴ found *HLA-B*1502* to be a risk allele for lamotrigine-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in Chinese populations, while *HLA-A*2402* was found to be a risk allele for both lamotrigine-induced SJS/TEN and maculopapular eruption in Chinese and Korean populations.

Singapore's population has a diverse, multi-ethnic make-up comprising representations of East Asian, Southeast Asian and South Asian ancestry. A recent study by Chan et al.³⁵ performed a deep interrogation of clinically significant genetic variants from 9051 Singaporean whole genomes. Of particular relevance were the findings that

51.0–77.2% of individuals across ancestries harboured alleles with actionable phenotypes in *CYP2C19*, and 31.1–47.2% of individuals carried actionable phenotypes in *CYP2D6*—both of which, as aforementioned, being involved in the metabolism of psychotropics including antidepressants and antipsychotics. Since 2013, genotyping for the *HLA-B*1502* allele prior to the initiation of carbamazepine therapy in patients of Asian ancestry has been considered standard of care with available subsidies for the genotyping test.³⁶

In addition to genetic polymorphisms, lifestyle or environmental factors, such as diet and exposure to traditional or alternative medicines, may also substantially modify the activity of drug metabolising enzymes.³⁷

Key recommendations

Strong recommendation that pharmacogenomic testing should not be routinely ordered in routine clinical psychiatric practice. Exceptions may include concerns about drug concentrations (due to metaboliser status) or potential severe adverse drug reactions. Pharmacogenomic testing should be mainly limited to the drug-gene pairs with established clinical evidence such as the antidepressants and *CYP2C19* and *CYP2D6*. If pre-existing pharmacogenomic testing exists for known drug-gene pairs, this information should be taken into consideration and discussed with patients during the selection of psychotropic medications.

Direct-to-consumer pharmacogenomic panels that assay multiple genes and analyse them via proprietary algorithms, are not presently recommended in our local psychiatric setting, due to limited and inconclusive available evidence on clinical outcomes. Pharmacogenomics is a rapidly advancing field and improved panels with fewer drawbacks may be developed in the future, which would warrant further evaluation of clinical utility. Studies investigating clinical effectiveness and cost-effectiveness of utilising pharmacogenomic testing in psychiatry is encouraged.

CONCLUSION

Recommendations

In line with the available body of evidence, we recommend that pharmacogenomic testing should be employed as an augmenting tool to guide medication selection and dosing in certain clinical situations, and not as part of standard or routine clinical practice. Clinical situations could include concerns about blood concentrations of a drug (due to metaboliser status) or significant adverse drug reactions. Examples of these include patients

who have failed multiple trials of medications or experienced significant adverse side effects even with low doses of medication. In the former case, patients may be ultra-rapid metabolisers, which necessitate higher doses of the affected drug or a switch to a drug not metabolised by the identified *CYP450* enzyme. For the latter, patients may be poor metabolisers and consequently have higher blood concentrations of the drug even at usual starting doses.

Pharmacogenomic testing should also be mainly limited to the drug-gene pairs with established clinical evidence such as the antidepressants and *CYP2C19* and *CYP2D6*, which can be found within the CPIC³⁸ or the DPWG³⁹ guidelines. Clinicians should also be aware that many of the drug-gene associations have not been evaluated for clinical outcomes. Examples of available resources include the FDA Table of Pharmacogenetic Associations¹¹ and Pharmacogenomics Knowledgebase (PharmGKB),⁴⁰ a curated repository of clinically actionable drug-gene associations and genotype-phenotype relationships.

Existing challenges to the adoption of direct-to-consumer pharmacogenomic panels include the variability of included genes across providers, lack of transparency in the proprietary algorithms and the lack of available studies evaluating populations of Asian ancestry.

The field of pharmacogenomics and its application to psychiatry is a promising one. Larger studies, such as the PSY-PGx Project⁴¹ and Ubiquitous Pharmacogenomics Project,⁴² and collaborations to study Asian populations will most certainly be welcome additions.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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