

The promise and challenges of pharmacogenomics in psychiatry

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Pharmacogenomics (PGx) is an expanding field within precision medicine that is poised to play a crucial role in optimising patient outcomes, particularly in the realm of psychiatry. The remission rate for the initial antidepressant prescribed in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was only approximately 30%, underscoring the need for more personalised approaches to prescribing.¹ For psychiatric patients who may show resistance towards pharmacotherapy, PGx offers promise in reducing adverse effects and enhancing therapeutic efficacy. Personalised pharmacotherapy provides reassurance and potentially mitigates the nocebo effects and somatic symptom exacerbation that are prevalent among these patients.

In this issue of the *Annals*, a consensus workgroup of Singapore psychiatrists developed practice recommendations for using PGx in psychiatry, based on a comprehensive review of current literature, with a focus on the Asian perspective.²

The majority of evidence supporting the use of PGx in psychiatry pertain to antidepressants. While more than half of high-quality randomised controlled trials recruited patients and failed to show a statistically significant change in clinical endpoints, recent meta-analyses indicate that PGx-guided antidepressant prescribing is linked to improved patient outcomes through pooling results, mainly in patients with moderate-to-severe major depressive disorder.³⁻⁵ Arnone et al. demonstrated that PGx testing in the treatment of depression was more effective than standard treatment in terms of improvement (odds ratio [OR] 1.63, 95% confidence interval [CI] 1.19–2.24); response (OR 1.46; 95% CI 1.16–1.85); and remission (OR 1.85; 95% CI 1.23–2.76).⁴ Similarly, Brown et al. found that patients receiving PGx-guided antidepressant therapy were 1.41 times more likely to achieve remission (95% CI 1.15–1.74, $P=0.001$) compared to those who were unguided.³ Wang et al. observed that the benefit of PGx testing was significant at

week 8 and week 12, but not at week 4 (when antidepressants have not reached their full benefit) and week 24 (when clinicians would have adjusted therapy according to clinical response).⁵ The International Society of Psychiatric Genetics Dutch Pharmacogenetics Working Group and the French National Network of Pharmacogenetics support the use of PGx testing and personalised dosing of antidepressants metabolised by Cytochrome P450 (CYP) 2C19 and CYP2D6. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC)⁶ provide recommendations for dosing adjustment or alternative antidepressants, such as serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants for CYP2C19, CYP2D6 and CYP2B6. Similarly, the U.S. Food and Drug Administration (FDA) makes recommendations for psychotropics metabolised by CYP2C19 and CYP2D6 on the drug label and table of pharmacogenetic association.⁷

While literature supporting the clinical utility of PGx in other disease states, such as psychosis, remains sparse, studies by Jukic et al.⁸ and Cui et al.⁹ provide robust evidence for the utility of CYP2D6-guided prescription for risperidone and aripiprazole. A meta-analysis by Saadullah et al. suggested that PGx-guided antipsychotic prescribing may improve symptom response and reduce side effects, emphasising the need for future randomised controlled trials with larger sample sizes for more definitive guidance.¹⁰ It is critical to note that in Singapore, testing for HLA-B*15:02 before initiating carbamazepine (a common treatment for bipolar disorder), is considered standard of care.

Goh et al. emphasised that while PGx testing is not yet recommended as routine clinical practice, it may be considered when there are concerns about drug concentrations or potential severe adverse drug reactions.² The group also recommended limiting PGx testing to antidepressants and CYP2C19/CYP2D6, and incorporating pre-existing

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PGx results into clinical decision-making—aligning with recommendations from international organisations (e.g. FDA, CPIC, etc.).

The evidence supporting PGx is primarily based on studies conducted in populations of European ancestry, with a significant gap in data from Asian populations. However, variants of pharmacokinetic genes like *CYP2C19* and *CYP2D6* are often coding and functional. In other words, regardless of Caucasian or Asian descent, a patient carrying a loss-of-function variant of a pharmacogene will typically have reduced activity of the encoded enzyme or transporter. While the prevalence of such variants may differ across genetic ancestries, their functional impact remains consistent.

The pharmacogenomic landscape in Asia reveals a higher prevalence of certain PGx variants that affect drug metabolism. For example, the allele frequency of *CYP2C19* loss-of-function variant is about 49–59% in Asians, compared to 22.8–28.6% in Caucasians. Similarly, the *CYP2D6**10 variant, associated with reduced enzyme activity, is found in 42.8% of East Asians, compared to 1.57% in Europeans.⁶ These genomic variations may lead to higher plasma levels of specific psychotropics in Asians, increasing the risk of adverse effects and necessitating dosage adjustments.

Direct-to-consumer PGx panels often aggregate and analyse genetic information, using proprietary algorithms to provide treatment recommendations. We agree with Goh et al. that the variability in gene selection and lack of transparency in algorithms present significant challenges to their widespread adoption.² The extensive list of genes offered on commercial direct-to-consumer panels may not be consistently associated with established clinical outcomes, adding cost and confusion to the interpretation of results. The lack of adequate regulatory oversight for direct-to-consumer PGx panels is also a concern.

Other than genomics, it is essential to consider other clinical factors that affect drug response. PGx test results should be integrated as part of a comprehensive clinical assessment, which includes evaluating the patient's overall health, treatment compliance, comorbid conditions and concomitant medications. For instance, hepatic impairment may affect drug metabolism and should be factored into the interpretation of PGx results. Furthermore, the patient's preference, cost of medications and perceptions towards medications also influence treatment outcomes. A holistic approach to patient care is crucial for achieving desired outcomes.

In Singapore, particularly at the National University Health System, a proactive strategy, known as

pre-emptive PGx, is being adopted. This initiative involves testing patients for a PGx panel curated based on local variants before clinical indications arise. As such, it eliminates the dilemma of “whether to test or not” and shifts the focus to “how to utilise the PGx information when it is available.” This approach is consistent with Singapore's broader trend towards embracing precision medicine. In future, as whole genome sequencing becomes more prevalent for other medical indications, PGx data could be extracted to optimise pharmacotherapy with minimal additional effort, further reducing the consideration for cost and logistics.

Pre-emptive PGx testing provides clinicians with genetic information upfront, enabling more informed decisions regarding medication selection and dosing. This may improve treatment outcomes, reduce trial-and-error prescribing and enhance patient safety.

Despite the potential benefits of pre-emptive testing, safeguards—such as robust data privacy measures, informed consent protocols, and clear policies for handling incidental findings—are required for its responsible implementation. To this end, pathways need to be developed to overcome logistical challenges such as data storage and appropriate handling of clinically relevant test findings.

To optimise the potential of PGx, medical students and clinicians should be educated about PGx to reduce inertia in using PGx to inform their practice. Conducting large-scale studies focusing on Asian populations to address gaps in ethnicity-specific data will instil confidence in the clinical applicability of PGx to the population in our clinicians. Policy-level changes, such as introducing subsidies for PGx testing, are necessary to improve accessibility and equity in resource-constrained settings. Finally, practical steps for integrating PGx into clinical practice include the development of decision-making algorithms, clinician training programmes, cost-effective PGx panels tailored to local genetic and clinical contexts, and resources for interpreting test results. The effort from Goh et al. marks the first step in this journey.²

PGx represents a promising frontier in psychiatric care, offering the potential for more personalised treatment strategies. Clinical benefits have been demonstrated for antidepressants and *CYP2C19*/*CYP2D6*. When available, this information should be incorporated into therapeutic decisions, aligning with practice recommendations from local psychiatrists² and international guidelines. Pre-emptive PGx, as part of the broader precision medicine framework,

may potentially transform psychiatric practice. Although the field is still evolving and fraught with challenges, ongoing research and clinical implementation will pave the way for more tailored interventions, improving the lives of patients with psychiatric disorders.

Declaration

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