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Pharmacogenetic testing in psychiatry: Perspective on clinical utility

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ABSTRACT

Pharmacogenetic studies the influence of inherited characteristics on medication. While different from pharmacogenomics, which is a study of the entire genome in relation to medication effect, their distinction remains inconsistent, and the two terms are used interchangeably. Although the potential of pharmacogenomics in psychiatry is apparent and its clinical utility is suboptimal, the uptake of recommendations and guidelines is minimal and research into PGx is not diverse. This article offers an overview of pharmacogenetics (PGx) in psychiatry, explores the difficulties, and provides recommendations on improving its applicability and clinical utility.

1. Introduction

Ever since Friedrich Vogel coined the word 'pharmacogenetics'(Vogel, 1959), research has advanced in this scientific field that explores how variations in specific genes affect the response to medicines. 'Pharmacogenomics', is understood as the study of the entire genome in relation to medication effects, it forms the basis of pharmacogenetics (Sutrop, 2004). Furthermore, pharmacogenetics has improved translational medicine by aiding specificity with drug advancement. Despite advances in the translation of pharmacogenetics to clinical practice, its application in Psychiatry however remains suboptimal, calling for multidisciplinary action.

This paper is a global collaboration between scientists, academics, and clinicians. We offer a current perspective on the state of pharmacogenetic testing (PGx) in psychiatry. This article includes an overview of its utilisation in mental health, barriers to utilisation and concludes with recommendations. Box 1.

(a) **The clinical utility of pharmacogenetic testing**

The clinical utility of a test may be determined by improvement in patient outcome, impact on prescribing pattern and cost-effectiveness of the test (Relling and Evans, 2015). Randomised Controlled Trials (RCTs) and non-RCTs inform implementation of PGx in clinical care. PGx recommendations exist for over 80 medicines, involving cytochrome P450 enzyme genes; others involve transporter genes and human leukocyte antigen (HLA) gene. However, clinical uptake of these recommendations remains low (Rollinson et al., 2020).

(b) **Cost-effective evaluations of pharmacogenetic testing**

Cost-effectiveness analysis (CEA) is an economic evaluation to achieve maximum value at the least cost. PGx-guided treatments could be evaluated to determine whether they are more effective

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at an acceptable extra cost (cost-effective) or lesser cost (cost-dominant or cost-saving) (Verbelen et al., 2017). PGx cost-effectiveness studies typically compare PGx-guided care to standard care (Karamperis et al., 2021; Sukri et al., 2022; Verbelen et al., 2017). The quality-adjusted life-year (QALY) assess outcomes by measuring quality of life with incremental cost effectiveness ratio, which compares net-cost of the evaluated intervention to its health benefits (Sukri et al., 2022). Proactive once-in-a-lifetime, multigene testing for several alleles with results integrated into electronic health systems are more economical than reactive, and single gene testing is similar in cost (Morris et al., 2022). Other factors affecting cost effectiveness are costs of patient management, treatment of adverse drug reactions (ADRs), population frequency of the variant and the clinical validity of the genetic biomarker (Sukri et al., 2022). Studies on cost-effectiveness of PGx in psychiatry cannot be generalised to the sub-Saharan African population a lack of universal health care means that most psychiatric medications are subsidised and paid for out-of-pocket of the individual (Abdulmalik et al., 2019). This suggests for further cost-effectiveness PGx studies from the African context.

(c) **Psychiatry pharmacogenomics**

Traditionally, psychopharmacological treatment involves multiple dose adjustments against patient response. In practice patient response depends in part on individual genetic factors. Many antipsychotics are metabolised by cytochrome P450 enzymes, mainly CYP2C19 and CYP2D6 (Hoffmann et al., 2014; Sheehan et al., 2010; Tom and Amy, 2007; Urichuk et al., 2008). CYP genes are highly polymorphic, and 62% of people across the globe have variations in CYP2D6 and CYP2C19 (Koopmans et al., 2021). Yuan etal., conducted a genome-wide association studies (GWAS)of antidepressant response in Han Chinese MDD patients (Yuan et al., 2022). They findings were "the GWAS significant locus is located at 6p12.3, in the upstream of CYP2AC1P, which is a pseudogene belong to cytochrome P450 family 2 (CYP2). This is empirically intriguing, as CYP2 is involved in the first phase of drug metabolism, and several other genes belonging to CYP2, CYP2D6, CYP2C9 and CYP2C19 are the most functionally important genes in pharmacogenomics (p.2).

Patients with extreme phenotypes, i.e., those with no or low activity or increased activity, have an increased risk of adverse events or treatment failure due to drug levels that are either too high or too low (Gaedigk et al., 2014, 2011). Therefore, gene variations affect the pharmacokinetics and pharmacodynamics of psychotropic medications. The pharmacokinetics of medications can be altered by genetic variations in coding the oxidative and conjugative phases of metabolism. Pharmacodynamic aspects are exemplified by adverse effects that are influenced by immunological variations in HLA (Hicks et al., 2020).

Pharmacogenomic studies have revealed the basis of some ADRs. Some ADRs are dose dependent while others are pharmacokinetic independent. Functional variants of the CYP2C19 enzyme are associated with ADRs following antidepressant use. Poor metabolisers have greater exposure to antidepressants, increasing their risk of gastrointestinal, neurological and sexual side effects (Cacabelos et al., 2021). Severe cutaneous adverse reactions (SCAR) are associated with genes encoding human-leukocyte antigens (HLA-B*1502 and HLA-A*3101) or drug-metabolising enzymes in new carbamazepine users (Bousman et al., 2019; Chang et al., 2020; Sung et al., 2020). Therefore, PGx testing should be considered as part of a comprehensive approach to ADR prevention. Genetic variations in CYP2C19 and CYP2D6 could affect psychotropic treatment outcomes. Antidepressant effectiveness is associated with genes such as SLC6A4 (serotonin transporter), HTR2A (serotonin 2A receptor), GRIK4 (glutamate ionotropic receptor kainate 4), and FKBP5 (FK506 binding protein 5). Antipsychotics are mostly metabolised by CYP450 enzymes. DRD2 gene variations are being explored for the antipsychotic response in individuals with psychosis. Side effects of mood stabilisers are linked to variations in HLA-A, and HLA-B genes. Testing genetic variations in CYP2D6, CYP2C19, CYP2C9, HLA-A, and HLA-B would be beneficial while prescribing psychotropics (Hicks et al., 2020). Though PGx can help clinicians optimise drug therapy in psychiatry, the costs of genetic testing should be weighed against the total (direct and indirect) costs for patients with mental illnesses (Alchakee et al., 2022). Furthermore, the contradictory results of genotyping studies, lack of PGx expertise in low- and middle-income countries (LMICs), lack of robust studies from LMICs, and complexity of mental illness, are incessant challenges for PGx in psychiatry, especially in LMICs (Kam and Jeong, 2020). Even though managing pharmaco-genomic studies with a large sample size is a difficulty for LMICs, future research can help improve long-term outcomes (Selvarajan et al., 2022).

(d) **Guidelines for psychiatrists for the use of PGx testing**

Several bodies are involved in the development of clinical guidelines and therapeutic recommendations for the implementation of PGx in clinical settings. They include the Dutch PGx working group (DPGW), clinical PGX implementation consortium (CPIC), Canadian PGX network for drug safety and others (Relling and Evans, 2015; Rollinson et al., 2020).

These guidelines are disseminated online by the pharmacogenomics knowledge base (PharmGKb) (McDonagh et al., 2011). However, the application of PGx in medication development and clinical practice is not well established (Kirchheiner et al., 2005). There remains uncertainty as to how to incorporate PGx testing into clinical practice as there are no regulatory requirements thus reducing clarity and impacting practice (Borden et al., 2021; Deverka, 2009).

(e) **Machine learning algorithms**

Machine learning (ML) is the study of computer algorithm that improves through experience (Cilluffo et al., 2021). This technique can be used to improve the accuracy and reliability of PGx results. ML helps design a genetic dosing algorithm, that are important as various factors determine the drug response. These factors include the presence of medical co-morbidities, different enzymatic activities, diverse genetics due to ethnic differences, and enormous genetic variants which could have an impact on protein function.

ML or artificial intelligence can improve the "trial-and-error" method of selecting psychotropic agents and has already been shown to have satisfactory performance in predicting drug response in depression (Cilluffo et al., 2021). ML may aid in integrating multiple factors influencing drug response, genotyping, and ADR, thereby optimising

Box 1
Recent clarification.

- The term pharmacogenetics covers the study of single genes
- Pharmacogenomics is used to describe the study of several genes (Berm et al., 2016).

medication selection and dosing for psychiatric medications at the point of care. There are disparities in PGx testing in LMICs due to technological capacity.

2. Conclusion

PGx factors influence the course, treatment response and prognosis of psychiatric disorders. Advancements in genome sequencing can contribute to the success of PGx and personalised medicine. PGx in psychiatry can offer an exciting opportunity for precision psychiatry. The allure of personalised medicine must be evaluated in line with the cost in a resource-constrained regions around the world. Theoretically, genetic variations affect both the effectiveness and safety of the medications. Consequently, as genetics research and Deoxyribonucleic acid (DNA) sequencing technology improves, the direct-to-consumer (DTC) genetic tests will have become less expensive, leading to the rapid growth of this industry (Miller, 2018). In limited resource settings, policy makers, researchers, mental health care providers and other stakeholders should ensure that patients are provided with access to necessary high-quality tests and proper clinical management with careful considerations of the potential ethical and practical implications. Hence, there is the need for further clarification of the clinical relevance of PGx testing in psychiatry, increased education of the scientific community on the relevance of PGx testing, along with the availability of standardised, clear and consistent guidelines and recommendations (Hicks et al., 2020).

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Declaration of Competing Interest

All authors declare no interest.

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