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GENOTYPE-GUIDED ANTIDEPRESSANT PRESCRIBING

TRANSFORMING THE MANAGEMENT OF DEPRESSION AND ANXIETY WITH PHARMACOGENOMIC TESTING

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INTRODUCTION

Antidepressant medication is a cornerstone in the management of depressive and anxiety disorders. However, identifying the most effective antidepressant treatment can be challenging. On average, less than half of patients are reported to respond to a firstline antidepressant, and a third of patients do not respond or tolerate two or more trials of subsequent antidepressants.[1] Each trial of a new antidepressant takes an average of 4–8 weeks to evaluate effectiveness, often leading to months, or even years, of trial-and-error odysseys.[1] As a result, many patients experience an increased burden of side effects, potentially serious adverse events and prolonged poorly treated disease.[1]

The completion of the Human Genome Project in 2003 yielded numerous discoveries and advancements related to genomics and other "-omic" fields.[2] Genetic variation in three pharmacogenes (*CYP2D6*, *CYP2C19* and *CYP2B6*) has been shown to account for a large proportion of the variability in response to several commonly prescribed antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs).[2]

PHARMACOGENOMIC TESTING

Pharmacogenomic testing (PGxT) has emerged as one of the first forms of precision or personalised medicine and can be used to inform medication selection and dosing decisions based on this unique interindividual genetic variation (Figure 1).[3] As an example, patients who are genetically classified as CYP2D6 poor metabolisers are at a much higher risk of experiencing side-effects like nausea, sleep disturbances and sexual dysfunction when prescribed SSRIs metabolised by this enzyme.[4] Growing evidence now supports the clinical benefit and utility of performing PGxT to guide antidepressant prescribing and improve clinical outcomes.[2]

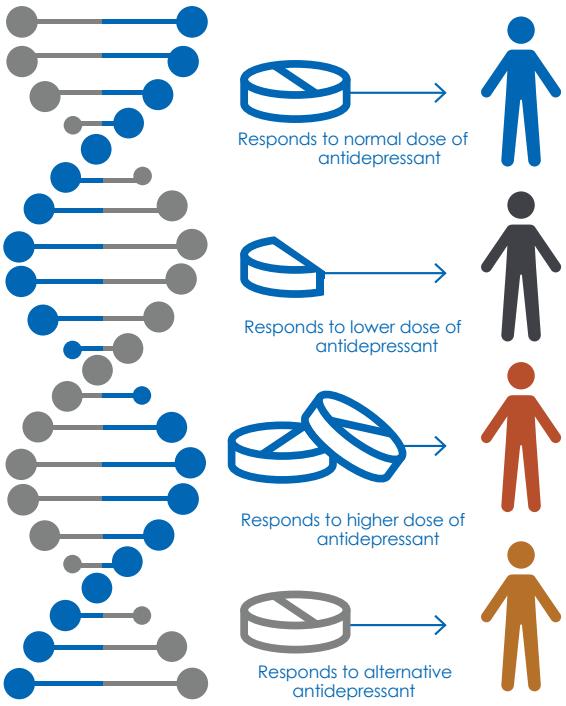

FIGURE 1: PERSONALISING ANTIDEPRESSANT DOSING AND SELECTION BASED ON INTERINDIVIDUAL GENETIC VARIATION

Ensuring clinical validity

The clinical validity of PGxT has been greatly improved by the availability of standardised clinical interpretation and reporting guidelines.[5] The Clinical Pharmacogenomics Implementation Consortium (CPIC) was established in 2003 and has now provided genotype-based dosing guidelines for 14 commonly prescribed antidepressants (Figure 2).[6] These guidelines are endorsed by several international pharmacological societies (including the American Society for Clinical Pharmacology and Therapeutics and the European Association for Clinical Pharmacology and Therapeutics), as well as the International Society of Psychiatric Genetics.[5]

The clinical utility of PGxT is also enhanced through the availability of the web-based clinical decision support software (ReviewGx™ and TreatGx™), as well as pharmacogenomics counselling services, all offered through Ampath Laboratories.

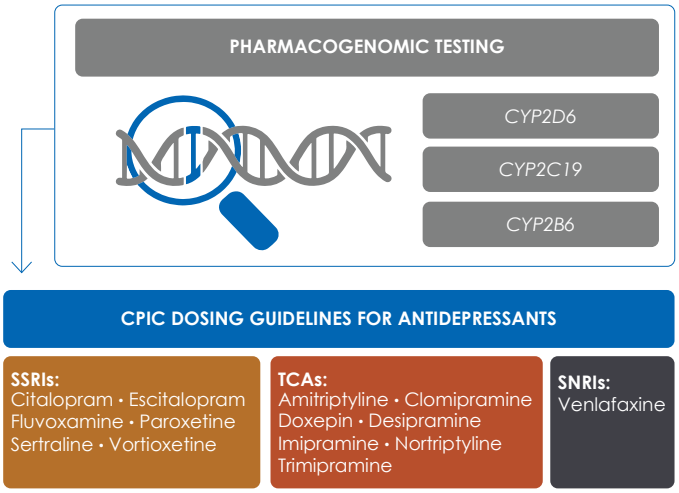

FIGURE 2: PUBLISHED GENOTYPE-BASED DOSING GUIDELINES ARE AVAILABLE FOR 14 COMMONLY PRESCRIBED ANTIDEPRESSANTS, BASED ON VARIATION IN THE *CYP2D6*, *CYP2C19* AND *CYP2B6* PHARMACOGENES.[5]

Improving analytical validity

Analytical validity refers to the accuracy by which PGxT can identify genetic variants that affect antidepressant metabolism. This is especially important in a genetically diverse country like South Africa. For genotype-based antidepressant prescribing, clinical laboratories typically interrogate *CYP2D6*, *CYP2C19* and *CYP2B6* variants that have known functional consequences (so-called actionable variants), and that are more prevalent in the general population. The Association for Molecular Pathology (AMP) has provided recommendations for minimum (Tier 1) and optional (Tier 2) alleles that should be tested for when genotyping *CYP2D6* and *CYP2C19* (Table 1).[7] The PGX250 pharmacogenomics assay performed at Ampath Laboratories tests for all of the Tier 1 AMP alleles, as well as the Tier 2 alleles with sub-Saharan African (SSA) population frequencies above 1%.[4]

EVIDENCE FOR CLINICAL UTILITY AND COST-EFFECTIVENESS

Numerous clinical trials, meta-analyses and systematic reviews have examined the efficacy and safety of PGxguided drug selection for the treatment of depression. In one of the most recent meta-analyses (published in July 2024) researchers showed that depressed patients receiving PGx-guided treatment were 41 to 78% more likely to achieve remission and 20 to 49% more likely to respond to treatment (as opposed to patients receiving treatment-as-usual).[8]

Genotype-guided antidepressant prescribing reduces health care costs by reducing adverse drug reactions (and the associated cost in managing these), reducing drug switches and adjustments, reducing the frequency of followup visits required, reducing the time to remission (thereby reducing hospital visits and lengths of admissions) and ultimately also improving patients' quality of life, resulting in improved productivity with reduced absenteeism.[9]

Using a microsimulation model, Canadian researchers were recently able to predict an estimated saving of C$956 million (C$4 926 per patient) for the Canadian mental health system over a 20-year period. In addition, they showed health gains of 0.064 life-years and 0.381 quality adjusted life-years per patient, all driven mainly by slowing or preventing the transition to refractory (treatment-resistant) depression.[9]

TABLE 1: ALL ALLELES LISTED HERE ARE INCLUDED IN THE PGX250 PANEL EXCEPT FOR *CYP2D621, *56 AND HYBRID GENES.**

CYP2C19 alleles		SSA population frequency
AMP Tier 1	*2	16%
	*3	<1%
	*17	17%
AMP Tier 2	*4	<1%
	*5	<1%
	*6	<1%
	*7	<1%
	*8	<1%
	*9	3%
	*10	<1%
	*35	3%
CYP2B6 alleles		**SSA population frequency**
Reduced/ no function alleles§	*6	37%
	*7	2%
	*18	6%

CYP2D6 alleles		SSA population frequency
AMP Tier 1	*2	17%
	*3	<1%
	*4	3%
	*5	6%
	*6	<1%
	*9	<1%
	*10	5%
	*17	20%
	*29	10%
	*41	5%
	*1x2	<1%
	*2x2	2%
	*4x2	2%
AMP Tier 2	*7	<1%
	*8	<1%
	*12	<1%
	*14	<1%
	*15	<1%
	*21	<1%
	*31	<1%
	*40	1%
	*42	<1%
	*49	<1%
	*56	<1%
	*59	<1%
	Hybrid genes	<1%

AMP - Association for Molecular Pathology
§ No AMP guidelines available

CONCLUSION

Genotype-guided antidepressant prescribing offers a transformative approach to the management of depressive and anxiety disorders by personalising antidepressant selection and dosing, thereby enhancing clinical efficacy. Pharmacogenomic testing for *CYP2D6*, *CYP2C19* and *CYP2B6* is available at Ampath Laboratories as part of our PGX250 panel, with results made available within 4 weeks.

For more information, contact pgx@ampath.co.za.