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Pharmacogenetic Testing to Optimise Antidepressant Treatment in Children and Adolescents: A Narrative Review

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ABSTRACT

Pharmacogenetics (PGx) focuses on examining and applying how genetic variability between individuals affects medication outcomes. By analyzing a patient's variation in genes linked to drug processing, PGx testing offers the potential to customize treatment in primary care and move beyond the traditional generalized prescribing model. In psychiatry, the use of PGx has produced encouraging findings, demonstrating improvements in therapeutic success as well as reductions in drug toxicity and adverse reactions. Although randomized controlled studies support its clinical value, numerous challenges still restrict its adoption. This review explores the use of PGx-informed decision-making for mental health management, with particular emphasis on treatment in children and young adults. In addition, it considers the clinical use of PGx testing, the concerns surrounding its introduction into youth psychiatric settings, and the obstacles that limit its routine integration in healthcare systems. Overall, this paper offers an extensive synthesis of current knowledge and applications of PGx in psychiatric medicine while highlighting the potential of genetic data to enhance individualized treatment for youth experiencing mental health disorders.

Keywords: Pharmacogenetics, Pharmacogenomics, Personalized treatment, Cytochrome P450, Drug metabolism, Youth psychiatry

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Introduction

Genomic variation exists within and across human populations, resulting in distinct phenotypes among individuals [1]. Genetic differences influencing drug metabolism and transport can significantly alter how a person responds to therapy. Recognizing this variability provides an opportunity to optimize medication choice and dosing in clinical practice, thereby improving quality of care [2, 3]. The investigation of gene variants related to medication metabolism and their biological impact on drug response is known as pharmacogenetics (PGx) [4], a discipline that shows growing potential as a clinical tool in precision and individualized medicine [5, 6].

Factors affecting drug effectiveness and toxicity can have major clinical and economic consequences, including preventable hospitalization. For the United States Food and Drug Administration's ten highest-selling medications, it has been estimated that between three and 24 patients fail to benefit for every individual who responds positively [7]. A recent PGx review cited Allen Roses, MD, stating that "more than 90% of drugs only work in 30% or 50% of people" [8]. Adverse reactions are believed to account for approximately 6.5% of hospital admissions [9, 10], and Australian reports suggest nearly 7.2% of admissions are linked to medication-related problems [11]. While multiple factors contribute, about four in five individuals are believed to carry genetic variants capable of altering drug safety and therapeutic benefit [12], and some estimates propose genetics may explain as much as 95% of treatment response [13]. Additionally, susceptibility to serious drug side effects differs by ancestry and geographic origins [14]. PGx aims to shift drug prescribing away from a generalized model toward a strategy tailored to the genetic profile of each patient [8].

Mental health conditions constitute a major proportion of disease burden in young people worldwide [15]. Individuals under 24 years old are especially vulnerable, with 30%–50% experiencing depression or anxiety that does not respond to standard therapy such as cognitive behavioral treatment or first-line medication [16, 17]. Without effective intervention, early mental illness can persist into adulthood and have long-lasting consequences [18]. At the same time, the rising prevalence of mental health issues has contributed to a sharp increase in antidepressant prescribing [19]. Between 2015 and 2019, de Oliveira Costa *et al*. documented that over 50% of Australian boys and girls aged 10–17 received a new antidepressant prescription. In light of increasing incidence and medication use, there is a pressing need to provide care that consistently achieves clinical benefit. PGx-guided antidepressant selection and dosing has been proposed as a way to enhance outcomes and reduce harmful drug reactions [20].

This review is divided into three major parts. The first outlines the principles of PGx and its clinical relevance, focusing on cytochrome P450 (CYP) enzymes involved in drug metabolism. The second section examines the role of CYP pathways in antidepressant processing and summarizes evidence from randomized trials evaluating PGx in mental health treatment. The final section discusses the use of PGx in young patients, identifying barriers that currently limit its adoption in primary care and highlighting gaps in the literature. Recommendations for future work needed to support the routine implementation of PGx in psychiatric care are also presented.

Pharmacogenetics

Definition of Pharmacogenetics and Pharmacogenomics

Pharmacogenetics (PGx) is a subfield within the broader area of "pharmacogenomics," which examines how differences in an individual's DNA (genotype) can influence their metabolic characteristics (phenotype) and consequently affect drug outcomes in terms of both benefit and toxicity [8]. Pharmacogenomics covers two principal dimensions of drug response: pharmacodynamics and pharmacokinetics. Pharmacodynamics focuses on how medications act on the body, while pharmacokinetics describes how the body alters the fate of a drug [21]. More precisely, pharmacodynamics investigates biochemical and physiological consequences triggered by a medication acting on its molecular target and the resulting cascade of effects [22]. Conversely, pharmacokinetics examines how the body absorbs, distributes, metabolizes, and ultimately eliminates an administered therapeutic compound [23]. These four pharmacokinetic steps are influenced by a person's genetic composition. By examining genetic variation affecting these processes through PGx testing, clinicians can anticipate how a patient may respond to different drugs and dosage levels. Consequently, PGx testing is being adopted as a clinical tool to refine medication selection and dosing by forecasting the interactions between genetic differences and pharmacokinetic behavior.

Cytochrome P450 enzymes and pharmacogenetic variation

Genetic variation can alter both pharmacodynamic and pharmacokinetic processes. Changes in gene function may modify how a medication is absorbed, distributed, metabolized, or excreted in an individual, all of which influence drug effectiveness and tolerance **(Figure 1)** [24–26]. Variants in genes controlling drug processing (PGx genes) are widespread, and recent evidence suggests that approximately 97.8% of the global population likely carries at least one actionable variant in a PGx-related gene [8]. Additionally, more than half of medications used in current clinical care rely on metabolism by PGx-associated genes and may be affected by one or more PGx variants [27, 28].

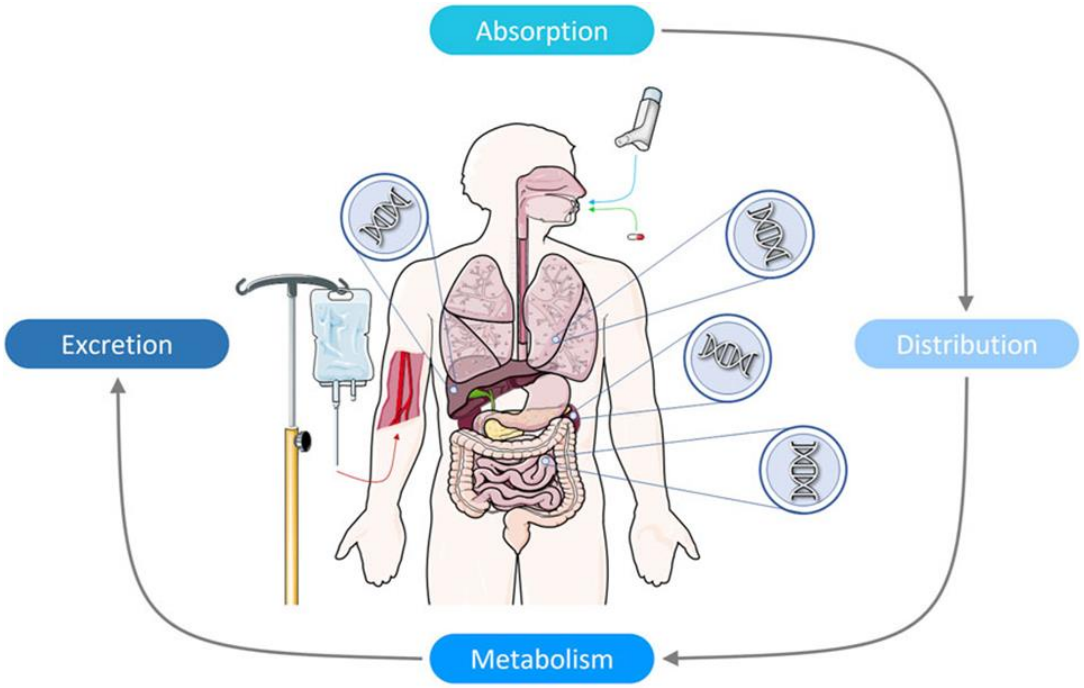

Figure 1. Pharmacogenetics investigates how genetic patterns influence pharmacokinetic and pharmacodynamic features, including genetic impacts on absorption, distribution, metabolism, and excretion across different therapeutic areas. Variants in genes encoding metabolic enzymes, transport proteins, and drug receptors—primarily expressed in the liver but also present in the lungs, kidneys, and intestinal tissues—can provide clinically useful insight into a person's metabolic status and anticipated therapeutic response.

Changes in genes that encode metabolizing enzymes, transporters, or receptor targets can significantly influence medication response [29]. Cytochrome P450 (CYP) enzymes are involved in over 90% of enzymatic drug-processing reactions and catalyze iron-dependent oxidation reactions that help convert lipid-soluble drugs into more water-soluble forms suitable for elimination [30]. The CYP gene family produces enzymes essential for the metabolism of pharmaceuticals and other external compounds (xenobiotics). These enzymes represent one of the most diverse metabolic systems in biochemistry and contribute substantially to differences between individuals in drug safety, response, and tolerability [31].

CYP genes are identified using a naming system consisting of a family number, a subfamily letter, and a numerical isoform designation (e.g., CYP2C9 or CYP1A2) [32]. At present, 57 CYP genes have been identified, but only six of them metabolize roughly 90% of all prescribed medications [33]. Many CYP genes possess functional polymorphisms that give rise to enzyme isoforms with different metabolic capacities, affecting the concentration of active drug available in the body [34]. Understanding how these genetic variations influence tolerability, predict drug–drug interactions, and affect therapeutic success is crucial. For example, data from Koopmans *et al*. (2021) [35] indicate that about 36% of the world population likely carries at least one actionable variant in the CYP2D6 gene, while approximately 62% are expected to have one in CYP2C19, altering how drugs metabolized by these enzymes are processed. PGx analysis enables classification of a patient's metabolic function into four primary phenotypes: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers [20]. Such classification supports individualized prescribing decisions rooted in a patient's genomic profile rather than generalized population norms. Because these variants are encoded in DNA, PGx testing is considered an efficient strategy to personalize medication therapy.

Large differences in CYP gene variants are observed not only between people as individuals, but also across populations with different ancestral backgrounds [14, 36]. For example, studies show that approximately 15–30% of individuals in Asian populations are classified as CYP2C19 poor metabolisers, compared with only about 3–6% of those with African, European, or Arab ancestry [37]. Conversely, CYP2D6 poor metaboliser status is estimated at roughly 7% among Europeans and Caucasian Americans, yet is found in only about 1% of Asian populations. Such uneven distribution of CYP alleles may create substantial differences in medication response between ethnic groups, potentially disadvantaging minority populations [37].

Genetic diversity in CYPs is unlikely to result solely from recent mutations but may instead reflect ancient adaptive advantages [38]. Although inherited genetic traits are widely recognised as major influences on drug metabolism [39–41], evidence suggests that exposure to environmental factors also contributed to the development of these metabolic systems. Diet, therefore, may be as relevant as ancestry when trying to understand an individual's medication response [42]. A wide range of foods and natural products—including fruits, spices, alcohol, herbal teas, and traditional remedies—can either suppress or stimulate CYP enzymes [43]. For instance, St John's wort (Hypericum perforatum), a herbal supplement commonly used to manage mild depression and known for good tolerability [44], is a strong inducer of CYP3A4. This leads to faster breakdown and reduced blood levels of medications processed by this enzyme, including sertraline, citalopram, and fluoxetine [45]. Because of this interaction, combining St John's wort with conventional antidepressants can pose serious risks.
These points emphasise that even though PGx testing is useful in precision prescribing, clinicians interpreting results must also consider the patient's cultural and ethnic background when planning treatment [14].

Pharmacogenetic testing in clinical practice

Although PGx testing has been commercially available for close to 20 years, widespread clinical use has been slow to develop. At present, such testing is mainly implemented in a limited number of specialist centres, predominantly located in North America and Europe1 [46–49]. This limited uptake is notable given that randomised studies have shown that PGx-guided prescribing can significantly improve patient response and tolerability [50]. The drugs most frequently associated with FDA PGx guidelines include agents for pain relief, blood clot prevention, and anti-inflammatory treatments [49].
Beyond improving medication outcomes, PGx implementation could also reduce economic burden. In Australia, approximately 400,000 people require hospital emergency treatment each year due to adverse reactions to prescribed medicines [51]. These reactions are estimated to cost the Australian health system around AUD ~$1.4 billion annually2, and since only about 6% of ADRs are actually reported, the true cost is almost certainly much higher [52]. Routine use of PGx screening could reduce the number of adverse reactions, prevent ineffective prescribing, and improve treatment efficiency [53, 54]. With simple and inexpensive cheek-swab genetic testing now widely available, PGx-based prescribing has become more accessible for routine patient care [55]. Broader integration of PGx is therefore important for supporting personalised care and reducing inequities, ensuring that treatment quality is not determined by genetic background [56].

Pharmacogenetics in the treatment of mental health

Mental health problems represent some of the most common illnesses in Western populations [57]. Before the COVID-19 outbreak, the World Health Organisation estimated that roughly one in eight individuals worldwide had a diagnosable psychiatric disorder, and rates increased by approximately 27% in subsequent years3. By 2030, mental health conditions are predicted to become the leading cause of global disease burden [58], with an estimated one in five people likely to experience at least one episode of mental illness during their lifetime [15]. Anxiety and depression are among the most frequently observed mental health diagnoses in primary healthcare and commonly occur together, often resulting in similar treatment pathways [59]. For mild and moderate presentations, psychological therapies are usually the first recommended treatment; however, individuals with more severe symptoms typically receive both psychotherapy and medication. Many second-generation antidepressants are also effective at reducing anxiety symptoms [60], allowing both disorders to be treated using one or more antidepressant drugs [61].

Understanding the role of cytochrome P450s in psychiatry

Antidepressant agents constitute the most commonly issued drugs for psychiatric conditions [62], yet their ability to reduce anxiety and depressive symptoms differs substantially between individuals [63]. Although many patients show remission within the first 2 months of therapy, more than half exhibit little benefit, and for some, symptom severity may actually rise [64]. Genetic variability in PGx-associated loci is thought to account for roughly ~42–50% of this broad clinical inconsistency [65, 66]. Even though more than 50 CYP genes participate in drug biotransformation [31, 33, 67], only a limited subset plays dominant roles in antidepressant metabolism **(Table 1)** [68]. Current estimates indicate that 24% of antidepressants depend on CYP1A2, 5% on CYP2B6, 38% on CYP2C19, 85% on CYP2D6, and 38% on CYP3A4 for metabolic conversion, though these fractions shift with variables such as sex, age, and population background [69]. Most medications in this class engage several CYP

enzymes, and each CYP can contribute to the metabolism of multiple antidepressant compounds [70]. Differences in allelic composition within CYP genes modify the rate and efficiency of enzymatic activity, influencing treatment effects, the risk of side effects, and clinical outcomes [71].

Table 1. Royal Australian and New Zealand College of Psychiatrists listed antidepressants, their primary mechanisms, and the dominant cytochrome P450 routes used in their metabolism, with secondary pathways noted in parentheses [68, 72–75].

Drug class	Generic drug name	Cytochrome P450 metabolism	Primary mechanism of action	References
Monoamine Oxidase Inhibitors (MAOIs)	Moclobemidea	CYP2C19 (CYP1A2, CYP2D6)	Blocks the enzymatic breakdown of monoamines A and B, resulting in elevated intracellular levels of 5-HT, NA, and DA	[76–80]
	Phenelzine	(CYP3A4, CYP2C19)	—	—
	Tranylcypromine	CYP2A6	Used as a later-line option because inhibition is irreversible	—
Tricyclic Antidepressants (TCAs)	Amitriptyline	CYP2C19, CYP3A4 (CYP1A2)	Broad pharmacologic effects; mainly reduces NA and 5-HT reuptake to increase synaptic availability. Greater specificity for NA transporters; some compounds block DA receptors	[81–83]
	Clomipramine	CYP2C19 (CYP1A2, CYP3A4)	Typically second-line because antagonism at histamine, muscarinic, and adrenergic sites causes unwanted effects	—
	Dosulepin	CYP2C19, CYP3A4, CYP1A2 (CYP2D6)	—	—
	Doxepin	CYP2C19, CYP3A4, CYP1A2, CYP2C9 (CYP2D6)	—	—
	Imipramine	CYP2C19 (CYP1A2)	—	—
	Nortriptyline	CYP2D6 (CYP1A2, CYP2C19, CYP3A4)	—	—
	Amoxapineb	CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP3A4	—	—
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram	CYP2C19, CYP3A4 (CYP2D6)	Selectively blocks 5-HT transporters, raising synaptic serotonin; minimal action on NA uptake	[82, 84–89]
	Escitalopram	CYP2C19, CYP3A4, CYP2D6	Promotes expression of neural growth factors (e.g., BDNF) and supports hippocampal plasticity	—
	Fluoxetine	CYP2D6, CYP2C9, CYP3A4 (CYP2C19)	Favoured as first-line owing to strong tolerability and safety	—
	Fluvoxamine	CYP2D6 (CYP1A2)	—	—
	Paroxetine	CYP2D6, CYP2B6	—	—
	Sertraline	CYP2B6 (CYP2C19, CYP2C9, CYP3A4, CYP2D6)	—	—
Serotonin–Noradrenaline Reuptake Inhibitors (SNRIs)	Desvenlafaxine	CYP3A4	Dual inhibition of NA and 5-HT uptake with limited effects on histamine, muscarinic, or	[90–95]

			adrenergic receptors; increases prefrontal DA	
	Duloxetine	CYP2D6, CYP1A2	—	—
	Milnacipran	CYP2B6, CYP3A4	—	—
	Levomilnacipran	CYP3A4 (CYP2C8, CYP2C19, CYP2D6, CYP2J2)	Commonly prescribed first-line	—
	Venlafaxine	CYP2D6 (CYP2C19, CYP3A4)	—	—
Selective Noradrenaline Reuptake Inhibitors (NRIs)	Reboxetine	CYP3A4	Selectively reduces NA reuptake, increasing NA and prefrontal DA while minimally influencing subcortical DA	[96–100]
	Atomoxetine	CYP2D6	—	—
	Teniloxazine	?	First-line medications known for energising properties and cortical stimulation	—
Serotonin Modulators	Trazodone	CYP3A4	High doses: blocks 5-HT reuptake via 5-HT2A/2C pathways	[74, 101–103]
			Low doses: antagonises 5-HT2A, adrenergic, and histamine receptors	—
	Vortioxetine	CYP2D6 (CYP3A4, CYP2A4, CYP2C19, CYP2C9)	Inhibits 5-HT transporters; acts as agonist at 5-HT1A/1B and antagonist at 5-HT3A/7	—
	Nefazodone	CYP3A4	Blocks 5-HT transporters, increasing cortical NA, DA, and BDNF	—
	Vilazodone	CYP3A4 (CYP2C19, CYP2D6)	Selective 5-HT reuptake inhibition with partial 5-HT1A agonism	—
Atypical Antidepressants	Agomelatine	CYP1A2 (CYP2C9, CYP2C19)	Enhances melatonin signalling; acts as melatonin agonist and 5-HT antagonist, raising DA and NA	[97]
	Mirtazapineb	CYP2D6, CYP3A4 (CYP1A2)	Inhibits 5-HT reuptake; blocks adrenergic receptors to elevate NA; reduces 5-HT activity to increase cortical NA and DA. Often used as a first-line agent	[104, 105]
	Mianserinb	CYP2D6, CYP1A2 (CYP3A4)	—	—
	Bupropionb	CYP2B6	Restrains NA and DA reuptake, prolonging their synaptic effects	[106]
	Maprotilineb	CYP2D6	Primarily inhibits NA and DA reuptake; also blocks histamine and adrenergic receptors; delays NA reuptake by inhibiting amine transporters	[107, 108]
NMDA–Glutamatergic Receptor Antagonists	Esketamine	CYP2B6, CYP3A4 (CYP2C9, CYP2C19)	Selective NMDA receptor antagonists that reduce calcium influx and raise prefrontal/hippocampal glutamate	[109]
	Ketamine	CYP2C9, CYP2B6, CYP3A4	Esketamine: non-competitive binding; Ketamine: competitive mechanisms	[110–112]
	Brexanolone	Non-CYP pathways	Boosts GABAergic inhibition by acting on GABAA receptors, increasing glutamate output	—

Atypical Antipsychotics	Aripiprazole	CYP2D6, CYP3A4	Partial D2 agonist affecting both presynaptic and postsynaptic pathways to enhance mesocortical DA; also alters 5-HT2A function	[113–118]
	Brexpiprazole	CYP2D6, CYP3A4	—	—
	Lurasidone	CYP3A4	Blocks D2 and 5-HT2A pathways to rebalance neurotransmission	—
	Quetiapine	CYP3A4 (CYP2D6)	D2 and 5-HT2A antagonism elevating cortical DA and 5-HT	—
	Olanzapine	CYP1A2 (CYP2D6)	Additional effects at 5-HT1A, histamine, and adrenergic receptors	—
	Risperidone	CYP2D6 (CYP3A4)	Includes muscarinic antagonism similar to olanzapine	—

NB: serotonin (5-HT), noradrenaline (NA), dopamine (DA).
a Reversibile.
b Bupropion is unicyclic; mirtazapine, mianserin, maprotiline, and amoxapine are tetracyclic.
c https://pubchem.ncbi.nlm.nih.gov/pathway/PathBank:SMP0000641
d https://s3-us-west-2.amazonaws.com/drugbank/fda_labels/DB11859.pdf?1553196718
e https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
?: Unknown metabolic pathway.

Although CYP3A enzymes are responsible for the metabolism of approximately ~30% of marketed drugs [68], the CYP2D6 and CYP2C19 genes hold the greatest clinical relevance in psychiatric prescribing. Both are extensively polymorphic and strongly influence how tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin–noradrenaline reuptake inhibitors (SNRIs) are processed [68, 119, 120]. Genetic divergence across these loci can substantially modify metabolic capacity and likely contributes to the wide spectrum of patient responses seen with antidepressants. The Pharmacogene Variation Consortium (PharmVar)[4] has catalogued more than 150 CYP2D6 alleles [121], with over 40 producing inactive enzymes, while other variants yield typical or elevated activity [122]. In a similar manner, over 30 CYP2C19 variants have been identified, of which only seven are classified as maintaining normal enzymatic capability [121]. Estimates suggest that approximately 10% of people are poor metabolisers for these pathways, and roughly 3% function as ultrarapid metabolisers [123, 124]. When pharmacogenomic testing is incorporated into routine care, clinicians can determine CYP2D6 and CYP2C19 phenotypes before initiating antidepressant therapy, which enables more accurate dosing and may enhance treatment success [125–127]. This point was illustrated by Jukić *et al*. (2018) [128], who assessed the relationship between CYP2C19 activity and escitalopram metabolism in 2,066 individuals. Participants classified as ultrarapid or poor metabolisers discontinued the drug more often—ultrarapid metabolisers due to inadequate symptom control and poor metabolisers because of adverse drug reactions (ADRs). Their findings support the conclusion that adjusting escitalopram doses according to CYP2C19 status may reduce ADRs and improve therapeutic outcomes in clinical environments [128].

When examining how CYP2D6 and CYP2C19 variants influence antidepressant metabolism in individuals with depressive disorders, research has shown that intermediate metabolisers tend to demonstrate more favourable outcomes, whereas ultrarapid metabolisers appear to carry an elevated likelihood of suicidal behaviour compared with other phenotypic groups [129]. Poor metabolisers, who have diminished enzyme functionality, typically accumulate higher serum concentrations of antidepressants than extensive metabolisers, which increases the possibility of adverse drug effects [130–133]. It is therefore essential, during antidepressant prescribing, to remain aware of interactions involving other medications processed by CYP2D6 and CYP2C19 in order to preserve overall therapeutic benefit. As an illustration, sertraline—a first-line SSRI—relies partly on CYP2B6 for metabolism and at 50 mg serves as a mild inhibitor of CYP2D6 [33]. Increasing the dosage from 50 to 200 mg transforms sertraline into a strong CYP2D6 inhibitor, thereby reducing the metabolism of additional CYP2D6-dependent drugs, including other SSRIs [134].

Investigations focusing on psychiatric polypharmacy and CYP-mediated drug–drug interactions indicate that the concurrent use of multiple psychotropic agents heightens the chances of harmful outcomes, hospitalisations, and has also been linked retrospectively to a higher incidence of suicidal actions [135, 136]. Retrospective evidence suggests that people who died by suicide were more likely to possess more than two active copies of the CYP2D6 gene compared to individuals who died from natural causes, signifying an ultrarapid metabolic phenotype that

may prevent attainment of therapeutic drug levels [129, 137]. Additional research not only relates ultrarapid CYP2D6 activity to suicide risk but also identifies a similar concern for ultrarapid CYP2C19 metabolisers and emphasises that such metabolic patterns, combined with polypharmacy, warrant consideration in suicide-prevention strategies for psychiatric patients [138].

Taken together, these and similar findings point to the usefulness of determining CYP2D6 and CYP2C19 metabolic profiles through PGx testing in clinical settings. Nonetheless, because PGx results currently provide probabilistic rather than definitive predictions, they should always be applied alongside clinical evaluation [139]. Much of the literature calls for continued research to expand knowledge regarding CYP-related influences on psychotropic drug metabolism.

Pharmacogenetic testing in clinical psychiatric practice

For many individuals with psychiatric disorders—including major depression—the path to identifying a suitable antidepressant often consists of multiple unsuccessful trials, each with insufficient or absent clinical benefit [140]. Approximately 60% of people with depression are thought to show only partial improvement with first-line antidepressants, and roughly one in three experience no measurable response at all [65]. Moreover, this same one-third who fail to achieve remission after two or more first-line medication trials are at increased risk of developing persistent depressive disorder [141]. Contributing factors may include unsuitable medication choices, adverse reactions, or disengagement from treatment following repeated therapeutic failures [142]. Importantly, response rates continue to decline with each subsequent drug trial: the likelihood of remission drops from 36.8% for the first treatment to 30.6% for the second, and then to 13.7% and 13.0% for the third and fourth trials, respectively [143]. PGx-guided prescribing has been proposed as a method to improve treatment outcomes for individuals who show poor response to multiple medications, potentially reducing ADRs and improving adherence [20].

Although many investigations have explored how PGx polymorphisms—including those in CYP2D6 and CYP2C19—shape psychiatric medication outcomes, relatively few randomised controlled trials (RCTs) have evaluated PGx testing as a tool for directing prescription choices. Two RCTs conducted by Hall-Flavin *et al*. (2012; 2013) [144, 145] reported that patients receiving PGx-based prescribing demonstrated significantly greater reductions in depressive symptoms after 8 weeks compared with individuals treated using standard clinical guidance. These trials incorporated PGx information from CYP2D6, CYP2C19, CYP1A2, and two serotonin-related genes (SLC6A4 and HTR2A). Meta-analyses involving 1,737 participants across five RCTs and 5,347 participants across 11 RCTs likewise indicated that PGx-guided prescribing promoted higher remission rates and quicker improvement in treatment-resistant depression [20, 146]. In a more recent RCT, Vos *et al*. (2023) [147] examined whether PGx-informed therapy could hasten the achievement of therapeutic TCA serum levels in 111 individuals. Those receiving PGx-guided treatment reached appropriate concentrations more swiftly and showed fewer or milder side effects. However, depressive symptoms did not differ between groups, suggesting that while PGx guidance may optimise pharmacokinetics, studies involving second-generation antidepressants might be necessary to clarify broader clinical impact.

Although the evidence discussed earlier indicates that PGx-informed prescribing could help personalise medication regimens for individuals with psychiatric illness, the literature still contains unresolved issues. In a systematic review, Solomon *et al*. (2019) analysed 16 publications from 2013–2018 to determine whether CYP2D6 and CYP2C19 testing could reliably forecast antidepressant effectiveness or the likelihood of ADRs [148]. Their review produced inconsistent conclusions: while PGx results appeared capable of identifying ADR risk in certain cases, it remained uncertain whether such findings would generalise to the wider population. Solomon *et al*. (2019) also pointed out that the inconsistent associations between PGx-guided therapy and reduced ADRs may stem from several factors [148], including inadequate statistical power, limited ethnic variation, and unrecorded use of complementary or herbal products. They emphasised that additional RCTs with robust sample sizes are required to resolve whether CYP-directed PGx strategies lead to clinically meaningful improvements.

In summary, although RCT data to date indicate that PGx guidance has the potential to support more precise medication selection and dosing for patients experiencing mental health disorders, further work is essential to fully understand its utility and to overcome current barriers to broad clinical integration. It should also be acknowledged that, despite advances in pharmacotherapy, only about 60%–70% of individuals treated with antidepressants achieve a favourable response [149, 150]. Continued investigation of PGx markers in people who fail to respond to treatment may assist in identifying alternative therapeutic options and help delineate genetic features associated with treatment-resistant depression [151, 152].

Clinical application of pharmacogenetics in youth mental health

Mental health concerns among young people represent a substantial public health issue. The most recent Young Minds Matter survey estimates that approximately ~600,000 Australian children and adolescents are living with mental health conditions such as depression5 [18]. Since the emergence of COVID-19, rates of depressive symptoms in young people have risen considerably [153], with nearly 39.6% of Australians aged 16–24 reporting mental ill-health in 20206. Additional increases in anxiety, isolation, and depressive mood have been noted among Australian secondary school students following the 2019 onset of the pandemic [154]. While there has been modest improvement since late 2021, prevalence remains high, and many young people still struggle to obtain adequate support7. Depression in adolescence is linked to poorer academic outcomes, impaired social development, and greater vulnerability to self-harm and risk-taking behaviours [18]. Young people who remain untreated frequently carry chronic symptoms into adult life, increasing the probability of long-term functional disability [155]. Evidence also shows that persistent depressive episodes between the ages of 12–17 can influence psychosocial development into adulthood, contributing to higher rates of early pregnancy, unemployment, and incomplete secondary education [156].

The continued escalation of depression among young people brings substantial lifetime costs related to mental health care, including hospitalisations, specialist services, disability supports, and subsidised psychotropic medications [157]. The economic burden of depression in Australia is currently estimated at AUD $43–70 billion per year8, incorporating both direct healthcare spending and reduced workforce participation due to illness. Given the increasing prevalence and financial impact of youth mental health disorders, reassessment of initial treatment strategies and service pathways is necessary to reduce long-term burden and improve the adequacy of care [158].

Guided antidepressant treatment in youth mental health

Although PGx-informed prescribing is well established in paediatric fields such as oncology and gastroenterology [159, 160], most PGx evidence informing mental health care is derived from adult studies and then extrapolated to younger populations [161]. Despite the current limitations, PGx testing in youth holds promise for reducing morbidity, minimising adverse reactions, improving therapeutic response, and potentially lowering the need for hospital admissions, readmissions, and overall healthcare expenditure.

Studies examining how metaboliser categories influence escitalopram use in paediatric groups present patterns comparable to those described by Jukić *et al*. (2018) [128]. Children and adolescents identified as CYP2C19 poor metabolisers tend to encounter more intense adverse reactions and are more prone to stopping escitalopram, citalopram, or sertraline altogether [162, 163]. Conversely, individuals classified as ultrarapid metabolisers typically show a more rapid clinical response to escitalopram and citalopram and often require shorter hospital stays once therapy begins. These outcomes align with the findings of Strawn *et al*. (2019) [164], who demonstrated that distinct CYP2C19 metaboliser phenotypes require different dosages of escitalopram and sertraline to achieve similar clinical benefit.

Research has also explored the relevance of CYP2D6 variation in antidepressant prescribing for younger patients. Fluvoxamine levels, for instance, persist longer in CYP2D6 poor metabolisers, necessitating dosing adjustments [165]. Likewise, fluoxetine is converted to norfluoxetine at a slower rate in poor metabolisers, resulting in elevated fluoxetine concentrations at equivalent time intervals compared with other metaboliser groups [166]. A recent review by Strawn *et al*. (2023) addressed common short- and long-term adverse effects associated with SSRIs and SNRIs in paediatric populations—such as gastrointestinal issues [167], progressive weight gain, and sexual side effects—and suggested that PGx-informed prescribing may help manage these reactions and guide safe withdrawal from second-generation antidepressants.

Although these data highlight the potential value of PGx-guided prescribing for antidepressant use in young people, other investigations have not demonstrated similarly positive outcomes. Namerow *et al*. (2022) summarise a prospective study by Vande Voort *et al*. (2022) in which 176 adolescents with moderate–severe major depressive disorder were allocated either to PGx-informed care or standard management [168, 169]. The goal was to determine whether multigene PGx panels influence clinical decision-making or improve patient outcomes in child and adolescent psychiatry. The study reported no meaningful differences between groups in depressive symptom change, adverse-effect load, or treatment satisfaction. Yet clinicians who used PGx information were more likely to prescribe non-first-line antidepressants, many of which have not shown reliable efficacy in paediatric depression. According to Namerow *et al*. (2022) [168], although PGx testing may not enhance treatment effectiveness, it may still guide drug selection in specific scenarios.

Given the inconsistent findings surrounding PGx use in youth mental health care, other dimensions of treatment may help clarify its value. Qualitative research shows that young patients often describe medication switching as stressful, with frequent changes perceived as discouraging trial-and-error processes that can heighten non-adherence [170]. Evidence also indicates that adolescents and older adults with depression face particularly high risks of poor medication adherence [171]. PGx testing may provide a mechanism to reduce this problem. Though research remains limited, one investigation found improved adherence across 39 medications when PGx information was used during prescribing [172]. By selecting medications that better suit individual metabolic profiles and avoiding high-risk options, genetically informed prescribing may strengthen adherence—a possibility that, while demonstrated in adults, could also benefit younger populations receiving psychiatric treatment.

Challenges for pharmacogenetic implementation in youth mental health treatment

Despite the encouraging results associated with PGx-supported prescribing, integrating genetic testing into standard antidepressant care poses multiple obstacles [173, 174]. Many countries—including the United States, Canada, the United Kingdom, and China—have elevated precision medicine to a major funding priority over the past 5 years, dedicating resources to expand personalised therapeutic strategies9,10,11. In Australia, Innovation and Science Australia outlined in 2018 a National Mission aimed at enabling widespread use of genetic-driven precision tools by 2030 to ensure the most appropriate treatment is provided from the outset12. However, both policy documents and scientific literature [175–183] identify substantial implementation barriers that must be addressed before precision approaches become routine.

In relation to PGx-guided prescribing specifically, even though its potential role in psychiatric care is increasingly recognised, unresolved challenges mean that PGx testing is likely to continue functioning primarily as a research-focused tool until these limitations are adequately managed [184, 185].

Lack of clinical guidelines for youth

At present, youth-specific, evidence-based recommendations for applying PGx in mental health care are scarce [186]. As a result, primary clinicians have limited agreement on how genetic results should shape drug choice or dose adjustments [187]. Although the Clinical Pharmacogenetics Implementation Consortium (CPIC) has recently issued guidance for interpreting PGx results in psychiatric prescribing [188, 189], children and adolescents were minimally represented in the studies informing these recommendations. CPIC therefore notes that the suitability of these guidelines for paediatric populations remains uncertain. In addition, most PGx studies in young people have used small samples and often lack replication, which restricts their usefulness for informing or validating CPIC recommendations.

Newer work suggests, however, that adult findings may still provide a foundation for paediatric PGx guidance. Historically, paediatric pharmacology has held that children differ substantially from adults physiologically and cannot be treated as smaller versions of them [190]. Rapid developmental changes and differences in organ maturity have contributed to the long-standing belief that paediatric drug effects and safety profiles diverge from those observed in adults; this has driven the need for child-specific dosing strategies. Yet pharmacokinetic research has proposed that, in some respects, children can be viewed as "scaled-down adults" [190, 191]. Anderson and Holford argue that adjusting adult doses by incorporating covariates such as body size, maturation level, and organ function may allow adult data to be used for paediatric dose predictions [192]. This raises an important question: if robust adult PGx evidence exists, is completely separate PGx efficacy research required in youth [193]? Stephenson notes that perceived differences in treatment response often stem from the absence of well-designed studies across paediatric age ranges rather than fundamental biological disparity [190]. Since most PGx studies originate from adult cohorts, further youth-focused and age-appropriate RCTs are essential to determine how reliably adult PGx evidence can guide prescribing in children and adolescents and to establish strong, clinically applicable guidelines [194, 195].

Experience and attitudes of general practitioners

General practitioners (GPs) are typically the first clinical point of entry in Australia's healthcare system, and mental health concerns remain among the most frequently managed conditions [196]. However, adopting PGx-informed prescribing in primary care introduces several difficulties. These include limited familiarity with PGx testing, uncertainty regarding its evidence base, and challenges integrating it into routine practice [181, 182]. Because PGx is still relatively new to mainstream medicine, many clinicians lack the training needed to interpret

genetic reports and apply them to treatment planning [197]. Numerous psychiatric medications are prodrugs that require CYP-mediated activation [33], while several SSRIs are active upon administration and rely on CYP enzymes for inactivation. A solid grasp of these pharmacological distinctions is crucial when using PGx information to minimise adverse drug reactions and drug–drug interactions.

A recent review by Ong *et al*. (2022) evaluated GP familiarity [198], perspectives, and experiences with PGx testing in primary care. Most GPs understood the basic scientific principles and acknowledged potential clinical advantages, but many felt unprepared to incorporate PGx results into prescribing decisions. Subsequent studies have confirmed that structured PGx education programmes can substantially increase GP confidence and comfort when ordering genetic tests [199]. These findings highlight a clear interest in PGx-guided mental health care among GPs and suggest that with adequate training, support, and clear procedures, primary care providers could feasibly integrate PGx testing into everyday practice.

Despite this enthusiasm, the absence of endorsed clinical guidelines continues to be a major deterrent for implementation. Many GPs report a need for additional research that translates PGx science into practical, clinically actionable frameworks. Ong *et al*. (2022) emphasise that understanding GP experiences and concerns is essential for developing realistic pathways for PGx adoption [198]. Ensuring that integration strategies reflect the actual needs and workflow of primary care settings is critical for successful uptake [200].

Attitudes and expectations of young people with mental ill-health

In addition to GP perspectives, existing literature has also examined how young patients understand and view PGx testing. Stancil *et al*. (2021) evaluated adolescent opinions on PGx and highlighted that research in this area remains sparse [201]. Their work underscored the need for more studies that clarify how youth interpret the purpose and value of PGx testing, along with effective methods for communicating test outcomes. Participants in the study expressed strong support for incorporating PGx-informed care into clinical practice. They recognised its potential usefulness in primary care, viewed the testing process as low risk, and believed PGx information could benefit both themselves and their peers [201]. The authors stress that involving young people directly in treatment discussions—including how PGx findings relate to drug selection—is essential for shared decision-making.

Societal expectations

Broader societal expectations regarding privacy, fairness, and economic implications present another layer of difficulty when attempting to normalise PGx-guided approaches12. Public concern over the handling of personal information has intensified, particularly within healthcare systems [202]. Although PGx testing offers numerous potential benefits, community trust depends on strong assurances of confidentiality. Moreover, equitable access must be prioritised so that precision medicine tools are available to individuals across diverse cultural groups and those living in rural and remote regions12. Financial considerations also remain a major obstacle; both patients and clinicians commonly identify the price of PGx testing as a deterrent [182]. Several studies show that cost is the dominant factor shaping patient decisions [203, 204], suggesting uptake would improve substantially if testing fees were reduced or subsidised through Medicare.

To address these systemic challenges and build public understanding of the potential benefits of PGx-guided mental health care for youth, meaningful engagement with the communities who stand to benefit is essential.

Conclusion

Mental health disorders continue to rise across Australia and other Western nations, with young people being particularly affected. Treating psychiatric conditions in youth is multifaceted, and inappropriate or delayed intervention can worsen symptoms and increase the likelihood of persistent mental health problems into adulthood. Despite advances in diagnostic approaches, symptom recognition, and pharmaceutical treatments, significant obstacles remain in the management of mental illness in young populations. PGx testing offers the possibility of improving therapeutic outcomes by reducing adverse drug reactions and their associated consequences. Current evidence indicates that awareness of a young person's PGx profile may help optimise treatment strategies and support recovery.

Although several barriers still limit the routine use of genomic testing in youth, ongoing developments in PGx have expanded access to DNA-based tools and PGx-informed prescribing. While initial studies suggest potential

benefits for young people, large, methodologically rigorous, age-specific trials are required to clarify inconsistent findings and determine how best to integrate PGx into everyday clinical practice. Additional research is also needed to understand how implementation can navigate behavioural, social, and financial barriers. Because most mental health care in Australia is delivered within primary care settings, evaluating PGx use specifically in this context is critical. Future work should therefore incorporate the perspectives of young patients alongside those of their primary care clinicians, ensuring that PGx-guided treatment evolves toward personalised, practical, and effective care for youth.

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