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Exploring the Efficacy of Pharmacogenomic Testing in Personalizing Antidepressant Therapy

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Abstract - ***Pharmacogenomic testing has the potential to transform the way depression is treated by tailoring antidepressant medication to each person's unique genetic makeup. In order to improve antidepressant medication selection, dosing, and patient outcomes, this research investigates how well pharmacogenomic testing works. To determine the efficacy of pharmacogenomic-guided therapy in comparison to conventional treatment methods, a systematic evaluation of relevant clinical trials, meta-analyses, and real-world data was performed. According to the results, pharmacogenomic-guided treatment has many advantages over traditional techniques, including a shorter time to remission, fewer side effects, and a greater response rate. This research highlights the promise of pharmacogenomics in improving the accuracy of antidepressant treatment, decreasing the need for trial-and-error prescriptions, and, in the end, alleviating depression patients' quality of life. To really reap the benefits of this tailored strategy, further study and wider use are required.***

Keywords: Pharmacogenomic Testing, Efficacy, Antidepressant Therapy

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1. INTRODUCTION

The substantial morbidity and economic cost of major depressive disorder (MDD) are symptoms of a mental disease. An estimated 326.2 billion dollars, a 37.9% increase over the 2010 estimate, was the economic burden of MDD in the USA between 2010 and 2018 (Greenberg, et al., 2015). As many as five percent of adults globally have depressive symptoms, according to the WHO. Treatments for major depressive disorder (MDD) that do not include pharmaceuticals include psychotherapy, TMS, and ECT. Despite the fact that all antidepressants for major depressive disorder (MDD) work in the same way, the tolerability profile of first-line pharmacologic alternatives like SSRIs or SNRIs makes them a popular choice. To address major depressive disorder (MDD), doctors may prescribe SSRIs or SNRIs in combination with other types of antidepressants, such as atypical antidepressants or tricyclic antidepressants (TCAs).

In the treatment of MDD, antidepressants show a moderate degree of effectiveness. An estimated 30% of patients have a complete disappearance of MDD symptoms after a single drug trial; however, this number drops significantly if additional medication trials fail (Rush, et al., 2006). Low remission rates need constant exploration of new treatment modalities to raise the bar for patient care. Personalised medicine, often known as pharmacogenomic-guided medication, is one alternative therapy method that has gained popularity in the last ten years.

One way in which pharmacogenomic-guided prescription might enhance results is by making it easier to detect genetic variations that affect metabolism. In such cases, polymorphism identification may aid prescribers in optimising the effectiveness and minimising side effects of these drugs. Prior to prescription antidepressants, pharmacogenomic (PGx) testing may be beneficial for individuals with CYP2C19, CYP2D6, and CYP2B6 polymorphisms.

Personalised dosage and pharmacogenomic testing are recommended for antidepressants metabolised by particular CYP enzymes by the International

Society of Psychiatric Genetics (ISPG), the Food and Drug Administration (FDA), and the Clinical Pharmacogenetics Implementation Consortium (CPIC). Pharmacokinetic factors vary from person to person due to genetic polymorphisms in CYP enzymes like CYP2C19 and CYP2D6, and the dosage recommendations are based on these variations. Even while certain genes and alleles, such SLC6A4 and HTR2A, may affect how well antidepressants work in the clinic, there isn't enough evidence to warrant screening for these genes and alleles to guide antidepressant prescriptions at this time.

Several factors have led to the current consensus that antidepressant-initiated patients should not undergo standard pharmacogenomic testing in the field of psychiatry. Because of clinicians' lack of awareness regarding PGx usage in psychiatry and their unfamiliarity with the testing, prescribers often remark that interpretation may be useless. Additionally, it is tricky to incorporate testing into existing workflows, and testing is costly and difficult to get (Jameson, et al., 2021). Patients who get PGx-guided prescriptions do not seem to have better clinical results, either. There was no change in clinical outcomes for individuals with MDD when PGx-guided prescription was compared to therapy as usual in several prospective clinical studies. But more randomised controlled studies have been added to the literature on PGx-informed medication in psychiatry in the last several years. In order to find out how PGx-guided prescription affected clinical outcomes such rating scale alterations, response, and remission in patients who were treated with antidepressants for MDD, this systematic review aims to assess the current prospective research.

1.1 Major studies in the field

In the 8-week randomised, patient- and rater-blind controlled trial called the GUIDED trial, which compared physician-guided antidepressant therapy selection (GUDED) with treatment as usual (TAU), 1,167 outpatients took part. At 27.2% and 24.4%, respectively, the two groups showed no significant difference in the key end measure of mean change on the Hamilton Depression Rating Scale among individuals who completed the trial up to week 8 ($p = 0.107$). There is reason to question the use of secondary outcome measures when combined with ineffective primary outcomes measures, as GUIDED was favoured by the response and remission secondary outcome measures (26% vs. 20%, $p = 0.013$ and 15% vs. 10%, $p = 0.007$, respectively).

In the 24-week open-label PRIME CARE Randomised Trial, researchers compared TAU (n = 978) with pharmacogenomic guided therapy selection (n = 966). In all, 44 patients seen at VA medical institutions were a part of the study. The teaching resources were designed to help with test interpretation and low-risk pharmaceutical prescriptions. The co-primary outcome variables were the percentage of prescriptions issued with a projected drug-gene interaction and the remission of depression (PHQ-9≈5). The pharmacogenomic-guided group was much more likely to receive treatments with low drug-gene interaction potential compared to those with moderate or high interaction potential. While pharmacogenomic treatment worked better than TAU in terms of remission rate throughout the first 24 weeks, the benefit was short-lived beyond that. It was determined that pharmacogenomic testing was not useful in a randomised clinical study of 304 persons with severe depression [4] carried out by Perlis et al. (2020). There was no statistically significant difference in symptom improvement or side effect load between the pharmacogenomic and TAU groups in the first randomised pharmacogenomic study of depression therapy in adolescents (n = 176). No evidence has been found to support the widespread use of pharmacogenomic testing to predict antidepressant response, according to a comprehensive study (Jameson, et al., 2021).

2. PHARMACOGENETICS OF ANTIDEPRESSANTS

Although antidepressants are a common choice for treating mood and anxiety problems, research has shown that only 50% of people feel better and 33% completely eliminate their symptoms after using these medications (Helton, & Lohoff, 2015). For several antidepressants, genetic factors seem to explain about 60% of the variation in responsiveness and side effects. Some examples of these drugs include monoamine oxidase inhibitors (MAOIs), tetracyclic compounds, SSRIs, SNRIs, TCAs, and noradrenergic and serotonergic modulators. For this reason, while selecting an antidepressant and establishing the right dose, it is essential to take into account an individual's genetic makeup. Research into the pharmacokinetic and pharmacodynamic effects of genetic variations on antidepressant drugs is ongoing, although much remains unknown. The genetic components of antidepressant response variability need to be better understood so that doctors may better fulfil the unique needs of their patients. Precision medicine has the potential to improve the rates of both the efficacy and safety of antidepressant treatments.

2.1. Variability of Pharmacokinetic

2.1.1. Cytochrome P450 Family

Antidepressants are among the many xenobiotics and pharmaceuticals that may be broken down by the enzymes that make up the CYP450 family. Even while most CYP450 enzymes metabolise certain psychiatric medications, some of the most essential ones include CYP2D6, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2C8, and CYP2C9. Some CYP450 enzymes can metabolise many substances simultaneously, whereas other CYP enzymes can only metabolise a single drug (Van Westrhenen et al., 2015). Van Westrhenen et al. (2015) suggests

that genetic variations impacting the activity of these enzymes might explain why antidepressant medication metabolism and reactions vary among individuals. According to Samardzic et al. (2017), the genes that code for cytochrome P450 enzymes tend to be extremely diverse. According to Samardzic et al. (2017), a substantial portion of personalised medicine research is on investigating how CYP polymorphisms affect medication metabolism. Though there are more than 2,000 variations in the CYP genes, only few of these SNPs have any discernible impact on the enzyme's activity. Drug metabolism may be characterised by one of four phenotypes: slow, moderate, widespread (normal), or ultrarapid cytochrome P450. Enzyme activity is influenced by these properties, which are in turn influenced by genetic variations. The CYP enzyme activity of PMs is lower than that of IMs due to genetic differences. They may have to take their antidepressant prescription less often or at lower doses because to the slower metabolism of the drug in PMs and IMs, which puts them at a greater risk of adverse drug responses. Enzyme activity and medication metabolism rates in NMs, however, are within typical limits. On the other hand, UMs have more active enzymes, which means that drugs are metabolised quicker. Therefore, in order for people with depression to get the intended therapeutic impact, it may be required to increase either the frequency or dosage of antidepressant treatment.

2.1.2. P-glycoprotein

P-glycoprotein, or P-gp for short, is an ABC transporter family member and a membrane transporter. Chromosome 7 is home to the ABCB1 or MDR1 gene, which codes for it. Drug distribution, absorption, and excretion are all helped along by P-gp, an efflux pump (Patel, et al., 2022). Among the many bodily tissues that contain P-gp are the blood-brain barrier, the intestines, the kidneys, and the liver. One possible explanation for the diminished effectiveness of certain medications is that P-gp blocks their passage across the blood-brain barrier. Because of individual differences in P-gp expression and activity levels, drug effects and interactions might differ from patient to patient. Different tissues and people have different amounts of P-gp expression, and this variance is partly due to genetic factors. According to Lazarowski and Czornyj (2011), P-gp substrate therapies may have an impact on pharmacokinetics and efficiency if certain ABCB1 gene variations are linked to changes in P-gp expression and activity. Escitalopram, fluvoxamine, paroxetine, amitriptyline, and imipramine are antidepressants that do not fall outside of P-gp's wide substrate specificity. Subsequently, when P-gp is deficient or nonexistent, these medications may build up in the blood, leading to greater concentrations and perhaps more harmful effects. Current antidepressants such as vilazodone, vortioxetine, and levomilnacipran do not work with P-gp substrates, as stated by Sarginson et al. (2010).

Magarbeh et al. (2023) note that some have pondered the possibility of a link between the efficacy of antidepressants and certain variants of the MDR1/ABCB1 gene. Studies have linked changes in P-gp activity to certain MDR1/ABCB1 polymorphisms. There has been a lot of study on the three most prevalent MDR1/ABCB1 mutations, according to Sarginson et al. (2010): C3435T (rs1045642), C1236T (rs1128503), and G2677T (rs2032582). Enhanced brain penetration of P-gp substrates and altered P-gp activity have been linked in recent experimental model studies to the 2677G > T mutation in the ABCB1 gene. Nonetheless, this does not seem to impact the production of P-gp proteins at the blood-brain barrier (Yamasaki, et al., 2022). Rather than the pace of response, genetic variations in the ABCB1 gene, such as the rs2235040 and rs4148739 polymorphisms, may be linked to when antidepressant medicine starts to work. Yamasaki et al. (2022) found that those with the ABCB1 rs2235015 GG genotype had a better reaction to antidepressants than those without the genotype. Additional study is necessary to comprehend the connection between genetic differences and pharmacological response, and it has not yet been shown whether pharmacogenetic studies on MDR1/ABCB1 can improve the results of antidepressant therapy.

2.2 A clinical use of pharmacogenetic testing

Despite PGx testing's almost 20 years on the market, it has been plagued by slow uptake into clinical practice. A limited number of premier clinics, particularly in North America and Europe, currently provide PGx testing, according to Volpi et al. (2018), Haidar et al. (2019), Maruf et al. (2020), and Smith et al. (2020). It is surprising that PGx testing is currently underused, even though it has been shown in clinical studies to greatly enhance the effectiveness and safety of pharmaceuticals (Pirmohamed et al., 2013). Analgesics, anti-inflammatory pharmaceuticals, and blood coagulation medications are the most often prescribed drugs with PGx recommendations authorised by the FDA (Smith et al., 2020).

When used to clinical practice, PGx may increase effectiveness and safety while decreasing costs to individuals and society as a whole. Phillips et al. (2014) found that prescription medication-related adverse drug reactions (ADRs) send almost 400,000 Australians to hospital emergency rooms annually. According to recent estimates, the Australian healthcare system spends around $1.4 billion per year on ADRs. According to Bailey et al. (2016), the actual cost to the Australian economy is likely far greater, since only 6% of adverse pharmaceutical reactions are recorded. Swen et al. (2023) and Verbelen et al. (2017) both found that systematic PGx testing would reduce the incidence and severity

of adverse drug reactions (ADRs), as well as simplify therapy and decrease the prescription of ineffective drugs. According to Blumberger et al. (2018), patients are now able to afford PGx-guided therapy thanks to simple buccal swab genetic testing. By integrating PGx testing into clinical practice, patient-centered treatment may be advanced and health inequities in populations can be addressed. That way, no matter a patient's family history, they will always have access to the most effective treatment (Hicks et al., 2019).

3. PHARMACOGENETICS AS A TOOL FOR MENTAL HEALTH TREATMENT

Mental health disorders rank high among the most common medical issues in Western countries, as reported by De Vaus et al. (2018). According to the World Health Organisation, the percentage of individuals dealing with a diagnosable mental illness increased from 1 in 8 prior to the COVID-19 epidemic to over 27% in the years before it. Mental health difficulties are projected to exceed all other sources of disease burden by 2030, affecting around 20% of the worldwide population (Friedrich, 2017; Mahi and Mann, 2018). Because they are so common, many primary care doctors treat their patients' anxiety and depression simultaneously (Tiller, 2013). Psychological therapy is the usual starting point for treatment of mild to moderate anxiety and depression, while patients with more severe symptoms generally get a combination of psychotherapy and medication. Antidepressants are often prescribed for both depression and anxiety since most second-generation antidepressants also have strong benefits in decreasing anxiety levels (Cassano et al., 2002; Ballenger, 2000).

3.1 Gaining insight into cytochrome P450s' function in mental health

Although antidepressants are the most often given medication for mental health disorders, there is still debate over how well they work in reducing depressive and anxious symptoms (Maslej et al., 2021). Although many patients have complete resolution within the first two months of therapy, more than half report just a partial improvement and, in very rare cases, even a worsening of their depression (Thomas et al., 2013). Metabolic differences due to gender, age, and ethnicity may influence the percentages for antidepressants (24%), CYP2B6 (5%), CYP2C19 (38%), CYP2D6 (85%), and CYP3A4 (38%). Radosavljevic et al. (2023) noted that while most antidepressants are metabolised by several CYPs, it is conceivable for a single CYP to be involved in the metabolism of many antidepressants. According to Van Westrhenen et al. (2021), changes in the allelic distribution of these CYP enzyme-encoding genes might impact the activity of the enzyme, which in turn impacts the effectiveness of drugs, treatment results, and the probability of potential adverse effects.

The CYP2D6 and CYP2C19 genes have been extensively studied in the area of psychiatry, but the CYP3A family is implicated in the metabolism of around 30% of all pharmaceutical drugs (Zemanova et al., 2022). The metabolic processes of tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-noradrenaline reuptake inhibitors are significantly influenced by the highly polymorphic CYP2D6 and CYP2C19 genes, according to researchers. There have been reports of this from Müller et al. (2013), Shalimova et al. (2021), and Zemanova et al. (2022). A person's reaction to an antidepressant could vary from person to person. One possible explanation is that variations in enzymatic and metabolic activity are caused by variations in people's genes. For example, the Pharmacogene Variation Consortium (PharmVar) 4 has identified 150 CYP2D6 allelic variants as of 2018 (Gaedigk et al.). About 40% of these variants code for enzymes that aren't active at all, whereas the remaining 60% code for enzymes that are active at normal or high levels. According to Bertilsson et al. (2002), this data was collected. According to Gaedigk et al. (2018), out of the over 30 CYP2C19 variants identified by PharmVar 4, only seven are known to preserve the enzyme's typical activity. Research has shown that phenotypes of CYP2D6 and CYP2C19 vary greatly across individuals throughout the world. For example, whereas 3% of the population is considered to have ultrarapid metabolism, only 10% is considered to have poor metabolism (Martis et al., 2013; Gaedigk et al., 2017). Potential benefits of PGx incorporation into clinical practice for antidepressant metaboliser status monitoring before medication prescription include improved treatment results and more accurate dosage predictions (Altar et al., 2015; Arranz and al., 2019; Greden et al., 2019). Jukić et al. (2018) found a notable variation in drug acceptability in their research on 2,066 people who were examined for CYP2C19-encoded enzymes and their escitalopram metabolism. Both therapeutic failures and adverse drug reactions (ADRs) were more prevalent reasons for discontinuation of escitalopram in individuals with a sluggish CYP2C19 metabolism compared to the other group. According to Jukić et al. (2018), PGx-guided medicine has the potential to enhance the therapeutic effects of escitalopram in practical situations by customising dose based on CYP2C19 status and creating unique treatment regimens for escitalopram. This approach has the potential to reduce the occurrence of adverse drug reactions (ADRs).

Researchers found that intermediate metabolisers had stronger reactivity to antidepressant medication in a study that examined the link between CYP2D6 and CYP2C19 alleles and antidepressant metabolism in persons with depression. Contrarily, compared to other metabolic phenotypes, those with ultrarapid metabolism had a higher suicide rate (Zackrisson et al., 2010). The research found that compared to extensive metabolisers, poor

metabolisers (those with reduced enzymatic activity) had higher serum antidepressant residual concentrations. This may have unintended consequences, according to studies conducted by Milosavljevic et al. (2021), Schenk et al. (2010), Chang et al. (2014), Huezo-Diaz et al. (2012), and others. It is critical to identify and account for antidepressant interactions when giving other medicines since these drugs are metabolised on the CYP2D6 and CYP2C19 pathways. A first-line selective serotonin reuptake inhibitor (SSRI) that is metabolised by CYP2B6 and, when administered at 50 mg doses, also marginally suppresses the activity of CYP2D6 is sertraline (Lynch et al., 2007). Sertraline becomes a powerful inhibitor when the dose is raised from 50 to 200 mg, as reported by Sproule et al. (1997). Antagonising CYP2D6 at this dosage, sertraline prevents the pharmacological metabolism of other medicines, including other prominent SSRIs.

Goffin et al. (2016) and Kessler et al. (2016) found that polypsychopharmacotherapy raises the incidence of adverse events, hospitalisations, and suicide behaviours, which are related to research on psychiatric drug-drug interactions and the significance of CYP genetic polymorphism. Study after study by Zackrisson et al. (2010) and Peñas-Lledó et al. (2012) found that the risk of having more than two active copies of the CYP gene CYP2D6 was higher among suicide victims. An ultrarapid metaboliser phenotype and the inability to attain pharmacological therapeutic potential are both associated with this gene. It is important to consider the phenotypes and polypharmacy of persons with mental illness in order to prevent them from attempting suicide. Peñas-Lledó et al. (2022) found that new research has linked rapid CYP2D6 metabolism to an increased risk of suicide and has even implicated those who metabolise CYP2C19 quickly.

These findings support the use of PGx testing for CYP2D6 and CYP2C19 metaboliser status in clinical situations, which have been shown in previous research. Always include PGx testing in your clinical evaluation; all it can do right now is give you a chance of possible vulnerabilities (Namerow et al., 2020). Additional study is needed to completely understand the role of CYP in the metabolism of psychiatric medications, as shown by most of the aforementioned studies.

3.2 Pharmacogenetic testing in clinical psychiatric practice

While scientists hunt for the best psychotherapy medications and doses, patients with mental health issues like depression may go through long stretches of ineffective treatment (Slomp et al., 2022). Crisafulli et al. (2011) found that first-line antidepressants only partly alleviate depression in around 60% of patients, and that about a third of those patients show no improvement at all. According to Kverno and Mangano (2021), persistent depressive illness might be the cause in one-third of cases where complete remission is not achieved following two or more courses of first-line antidepressants. Possible causes include pharmaceutical errors, adverse drug reactions, and, after many treatment failures, a failure to adhere to prescribed therapy (Howes et al., 2022). According to Rush et al. (2006), the remission rates for the first two medication trials were 36.8% and 30.6%, respectively. The third and fourth trials had rates of 13.7% and 13.0%, respectively, indicating that this trend continues with each successive antidepressant given to a depressed patient. According to Bousman et al. (2019), patients who have shown resistance to several antidepressants might potentially benefit from PGx testing and informed prescription. This could enhance treatment response and outcomes by reducing the likelihood of drug-related adverse effects and patient non-compliance.

Several research have investigated the potential that PGx gene polymorphisms impact the effects of psychiatric medications, following in the footsteps of investigations into CYP2D6 and CYP2C19. The use of PGx testing as a technique for medication guidance prediction has not been extensively studied in randomised controlled trials (RCTs). Patients who received PGx-guided treatment and tailored prescription had a significantly greater reduction in depressive symptoms after 8 weeks of antidepressant treatment compared to those who were treated according to standard clinical guidelines, according to randomised controlled trials (RCTs) conducted by Hall-Flavin et al. (2012) and Hall-Flavin et al. (2013). Some of the genes used to compile this information are CYP2D6, CYP2C19, and CYP1A2, in addition to the two genes that determine the activity of serotonin transporters (SLC6A4) and receptors (HTR2A). In individuals with difficult-to-treat depression, two recent meta-analyses compared conventional therapy to PGx-guided treatment with personalised prescription and dosage. The former showed better remission rates and reaction speeds. In Bousman et al. (2019) and Wang et al. (2023), researchers looked at 1,737 and 5,347 individuals, respectively, across five and eleven randomised controlled trials. The efficacy of standard of care therapy and PGx-guided treatment was assessed in a recent randomised controlled trial (RCT) by Vos et al. (2023) using the time it took for 111 individuals to reach therapeutic levels of TCA serum. Patients treated with PGx-guided therapy had fewer and milder adverse effects and reached therapeutic TCA concentrations quicker than controls, according to the study. Although PGx-guided therapy was helpful, symptoms of depression did not improve. Future research should include second-generation antidepressants in addition to tricyclic antidepressants (TCAs).

A number of concerns remain unsolved in the literature, despite the fact that the research listed above demonstrate potential for PGx-guided therapy to customise pharmacological therapies for

individuals with mental health disorders. For their 2019 analysis, Solomon et al. analysed 16 papers published between 2013 and 2018 to see whether PGx testing for CYP2D6 and CYP2C19 may foretell antidepressant response or adverse drug reactions. Although the study's inconsistent results may not be generalisable to a wider population, they do indicate that PGx testing may be able to predict ADRs in certain people. There can be a number of reasons why there is no evidence that PGx-guided therapy reduces ADRs, as Solomon et al. (2019) pointed out. Such problems include, but are not limited to, small sample sizes, under-representation of marginalised groups, and the unregulated use of CAM in combination with conventional therapy. To learn more about the potential benefits of CYP PGx-guided treatment for mental health, larger randomised controlled trials are needed, according to Solomon et al. (2019).

In conclusion, PGx-guided treatment may help mental health patients make educated choices about medication dosage and selection, according to evidence from randomised controlled studies. Still, we need further research to fully understand this method's benefits and identify the obstacles to its broad healthcare adoption. Notably, although antidepressant medication has shown encouraging outcomes in treating depression and anxiety, it is crucial to acknowledge that this therapy is effective for only 60% to 70% of patients (Kennedy and Giacobbe, 2007; Al-Harbi, 2012). The genetic profile of treatment-resistant depression should be better understood with further study of the PGx profiles of patients whose depression does not improve after medication (Fabbri et al., 2021; McCarthy et al., 2021). This, in turn, could guide the selection of alternative treatments.

4. PHARMACOGENETICS IN YOUTH MENTAL HEALTH: CLINICAL APPLICATION

According to the most current data from Young Minds Matter (Goodsell et al., 2017), over 600,000 children and adolescents in Australia are impacted by juvenile mental illness, which is a major issue in public health. Approximately 40% of Australians between the ages of 16 and 24 will report suffering from a mental disorder in 2020, a figure that has risen sharply since the start of the COVID-19 epidemic (Racine et al., 2021). Australian high school students also reported an increase in anxious thoughts, feelings of loneliness, and depression symptoms when the pandemic broke out in 2019. This information comes from Houghton et al. (2022). There has been progress since the year's end, but many young people still suffer from mental illness and lack access to therapy and support. Social development and academic success are two quality-of-life outcomes that are negatively impacted by adolescent depression. Additionally, self-injury and hazardous conduct are more likely to occur (Goodsell et al., 2017). Adolescents with untreated depression are more likely to have impairments and symptoms of depression throughout adulthood, as well as an increased risk of acquiring disabilities connected to depression (Ghio et al., 2015). According to studies (Clayborne et al., 2019), if a person has persistent depression between the ages of 12 and 17, their chances of enduring psychosocial consequences that persist into adulthood are higher. The rates of unintended births, unemployment, and students not completing high school are all impacted.

Along with the increasing number of depressed youngsters, the lifetime healthcare expenditures associated with mental health services have been on the rise. These services include visits to psychiatry and other allied health specialists, hospital stays, disability support programs, and subsidised medication (Cook, 2019). Depression is predicted to cost the Australian economy between $43 billion and $70 billion per year in healthcare expenditures, lost jobs, and unemployment possibilities. Urgently reevaluating present care routes and commencing treatment options are necessary to reduce the social and financial burden of juvenile mental health difficulties and ensure they get the attention they need (Le et al., 2021).

4.1 Youth mental health and guided antidepressant therapy

Most PGx research on mental health have been done on adults and their findings have been generalised to young people, even though PGx-guided prescribing is widespread in paediatric oncology and gastroenterology. Paediatric PGx-guided therapy has its limits, although PGx testing has promise for improving medication adherence, reducing hospitalisations and readmissions, and cutting treatment-related costs, adverse events, and complications.

The results of Jukić et al. (2018) about the link between escitalopram and metaboliser status in youth are supported by these research. Users with a poor CYP2C19 metaboliser status are more likely to cease use and have more severe adverse drug effects while using escitalopram, citalopram, or sertraline, according to new study (Aldrich et al., 2019). In addition to requiring less time in the hospital after drug administration, ultrarapid metabolisers had a faster body reaction to citalopram or escitalopram. In accordance with Strawn et al. (2019), we discovered that different CYP2C19 metabolisers necessitated different dosages of sertraline and escitalopram to sustain the therapeutic advantages of these drugs. Studies examining the role of CYP2D6 polymorphisms in the prescription of antidepressants to young people are also in the works. For instance, since CYP2D6 poor metabolisers' concentrations stay higher for a longer length of time, Chermá et al. (2011) states that these individuals should modify their fluvoxamine dosage accordingly. Norfluoxetine is the active metabolite of fluoxetine, and metabolisers with poor CYP2D6 activity also have trouble converting fluoxetine to this one. Gassó et al. (2014) found that fluoxetine concentrations were greater in poor metabolisers

compared to other metabolisers at the same time periods. The incidence of short-term and long-term adverse drug reactions (ADRs) in younger patients using SSRIs and SNRIs was recently investigated by Strawn et al. (2023). Some of the adverse drug reactions (ADRs) that might happen in young individuals on second-generation antidepressants include gaining weight, sexual dysfunction, and acute gastrointestinal issues. A PGx-guided treatment could be useful here.

Antidepressant drug PGx-guided therapy may be useful in the treatment of mental disorders in adolescents and children. But the results of these investigations are not uniformly encouraging. A prospective research examining depressive adolescents receiving PGx-guided therapy was examined by Namerow et al. (2022) in their assessment. Finding out whether PGx testing panels may improve mental health outcomes in paediatric psychiatric practice was the main goal of this investigation. 176 adolescents diagnosed with moderate to severe major depressive disorder were randomly assigned to either treatment as usual or therapy guided by PGx. In terms of symptom relief, side effect burden, and satisfaction, there was no discernible difference between the two groups. Regardless, the research did find that PGx testing did lead healthcare practitioners to give teens ineffective non-first-line antidepressants. It is possible that PGx testing will not increase the therapy's effectiveness. There is mounting evidence that PGx testing might be beneficial for some prescription medicines, as stated by Namerow et al. (2022).

Given the conflicting data about the effectiveness of PGx testing in adolescents with mental health issues, it is crucial to explore other domains of antidepressant treatment where PGx led treatment might advance the existing paradigm. According to a qualitative research that looked at how young people felt about medicine, some of them may not take their medication as recommended since switching antidepressants is a frustrating and hard process of trial and error (McMillan et al., 2020). Taking medicine as directed is increasingly common among patients of all ages, but especially those suffering from severe depression, according to recent studies (Gast and Mathes, 2019). When it comes to these challenges with adherence, PGx offers an intervention method. Despite the promising results of PGx-guided therapy on medication adherence, additional research is required to draw firm conclusions. One study found that patients who had PGx testing were more likely to take their prescriptions as prescribed. This research demonstrates that genetically informed care has the potential to improve medication adherence via the use of PGx testing to provide more personalised medicines and the avoidance of drugs that are not essential or may be hazardous. The results of this research suggest that personalised therapy in children may reduce rates of mental health concerns and raise rates of medication adherence, even though the study focused on PGx-guided treatment in adults.

4.2 Challenges for pharmacogenetic implementation in youth mental health treatment

The difficulties of employing genetic testing to direct the prescription of antidepressants for individual patients remain, despite the promising results of PGx-guided therapy (Pinzón-Espinosa et al., 2022). Governments throughout the globe have taken an interest in and shown support for the idea of precision medicine, which provides individualised treatment. The US, Canada, China, and the UK are among the countries that have pledged to implement this plan 9-11 and have achieved great strides in the last five years. In 2018, the non-governmental group Innovation and Science Australia, which advocates for sustainable economic growth and social benefits, established the ideal National Mission. By the year 2030, it hopes to have personalised treatment plans based on individuals's genetic composition and provide the appropriate treatment to the right people the first time. The policies and other scientific studies make it clear that there are major obstacles that must be overcome before precision medicine techniques can be used in everyday clinical practice (Goodspeed et al., 2019). No matter how quickly it is being used in personalised psychiatry, PGx testing will probably still be used for research purposes inside PGx-guided therapy until these obstacles are removed (Bousman et al., 2017).

4.2.1 Lack of clinical guidelines for youth

Primary care doctors can't agree on how to utilise genetic testing to choose and dosage medications for adolescents' mental health since there are no evidence-based recommendations for the use of PGx in this population. It should be noted that despite the recent publication of guidelines on the interpretation of PGx testing for psychiatric medication, numerous drugs included in the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations did not incorporate adequate studies involving children and adolescents. There must be proof that the suggestions are useful for paedeatric patients in general, according to the CPIC. Furthermore, these CPIC guidelines cannot be informed by the few replicated PGx research in juvenile psychiatry. New evidence, however, points to the possibility of using adult data to guide PGx therapy approaches for youth. It has long been believed in paediatric pharmacology that children are not miniature adults. A child's body and organ systems undergo many stages of fast development and growth, during which they operate differently from those of an adult. It has long been believed that children may have distinct impacts and safety profiles when taking medications, which is why separate doses and prescriptions are needed. But research on the pharmacokinetics of children has shown that, under some settings, they may be seen as little adults (Anderson and Holford, 2013). In their

contentious but crucial explanation of how to scale pharmaceutical dosages from adults to children, Anderson and Holford alter dosages according to demographic parameters including height, maturity, and organ function. If this is so, how important is it to have independent proof of effective PGx-guided therapy in children, taking into account the results in adults (Barker et al., 2022)? The lack of sufficient research on these substances in young populations of varying ages is the root cause of the widely held idea, according to Stephenson (2005), that children and adults react differently to drugs. Stephenson maintains that children's responses to medications are fairly similar to adults'. Since most PGx studies have been done on adults and then extended to kids, we need to know how reliable adult PGx are for paediatric medicine dosages. In order to establish a strong evidence-based benchmark for mental health therapies, further randomised controlled trials comparing research with adults and adolescents, as well as PGx-guided therapy in clinical settings, are required, theodores (2013).

4.2.2 General practitioners Experience and attitudes

Mental health disorders are among the most prevalent medical concerns seen by primary care physicians (PCPs), and many Australians' first experience with the healthcare system is with their PCPs. Nevertheless, PGx-guided mental health treatment presents primary care practitioners with a number of obstacles. Not knowing much about PGx testing, having trouble incorporating it into the current procedure, and having little data to support its use are all obstacles. The findings of PGx testing might be difficult for healthcare practitioners to comprehend and incorporate into treatment choices due to the topic's relative novelty in mainstream medicine. Many psychiatric drugs are transformed from their inert prodrug state into an active one via the action of cytochrome P450 (CYP) enzymes. The metabolism of medicines, including many SSRIs, is dependent on CYP enzymes. This process is vital for the deactivation of active compounds. If you want to make sure your patients are safe and avoid ADRs (adverse drug reactions) caused by drug-drug interactions, you need to know all the psychiatric medications on the market and how to interpret PGx test results correctly. To better understand primary care general practitioners' (PGx) knowledge, viewpoint, and utilisation of PGx, Ong et al. (2022) conducted research. While most GPs got the concept and could see the benefit of PGx testing, many were still confused about how to incorporate genetic results into treatment plans, the study found. According to a recent study by Preys et al. (2023), primary care practitioners, including GPs, feel more at ease ordering PGx tests for their patients after participating in education and training programs. These positive findings show that there is excitement for PGx-guided therapy in GP offices, which is great news since it suggests that primary care practitioners may incorporate PGx testing into their clinical practice given the right resources.

Some primary care physicians have voiced the need for more study into the best ways to integrate new genetic technologies into patient care, despite the fact that the aforementioned studies show a clear comprehension of the benefits of PGx testing. Further investigation into this issue may be useful in formulating standards for PGx testing. The need of fully comprehending GPs' knowledge, attitudes, and experiences with genetic testing is highlighted in the review by Ong et al. (2022). To successfully incorporate PGx testing into clinical practice, it is crucial to collect this data and adjust the integration to meet the needs of primary care practitioners (Aboelbaha et al., 2023).

4.2.3 Young people with mental ill-health Attitudes and expectations

Research has shown that patients are comfortable and knowledgeable with PGx testing, which supports the views of primary care physicians. Due to a dearth of literature on the topic, Stancil et al. (2021) sought to fill the gap by investigating how teens feel about PGx testing. Based on the findings of this study, there is an immediate need for further research on the significance and relevance of PGx testing among young people and the best ways to communicate test results to this age group. All of the young people who took part in this survey felt that PGx-guided therapy should be available in hospitals. Testing was considered safe, they knew how important it was for primary care, and they felt it would benefit their colleagues and themselves (Stancil et al., 2021). According to Stancil et al., it is crucial to include youth in decision-making and to have transparent conversations with them on the implications of PGx test findings on any medicine they may be given.

4.2.4 Expectations from society

Lastly, a barrier to standardising prostate cancer therapy might be cultural norms around data privacy, equality, and economic values. 12. The delicate topic of healthcare data privacy has gained more and more attention as of late (Vimalachandran et al., 2020). Beyond the clear advantages of PGx testing, protecting individuals' privacy will increase public trust in the use of genetic data. No one's race or location should determine whether they have access to precision medical resources. 12. Both patients and healthcare providers are deeply concerned about the expense of PGx testing, according to research (Jameson et al., 2021). Medicare might encourage more people to get PGx testing by lowering or subsidising its costs, as several studies have shown that cost is the most important factor impacting patients' decision making (Liko et al., 2020).

The communities that stand to gain the most from PGx-guided therapy should be the focus of research efforts aimed at improving children's mental health outcomes. By doing so, they will be better able to

comprehend their concerns, identify their requirements, and dispel myths around the technology.

5. CONCLUSION

Pharmacogenomic testing has the potential to assist in the personalisation of antidepressant medication, according to the findings of this research. The many benefits of pharmacogenomic-guided therapy over traditional treatment methods include improved response rates and fewer adverse effects caused by the medicine's genetic tailoring. By eliminating the need for ad hoc methods, clinical practice that combines pharmacogenomic testing might enhance depression treatment. To address existing concerns and ensure widespread use of pharmacogenomic testing by mental care practitioners, further research is necessary, while the results indicate promise.

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