7-25-2024

Assessing Utilization and Outcomes of Pharmacogenomic Testing Among Children and Adolescents in Outpatient Psychiatric Treatment: A Quality Improvement Project

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Assessing Utilization and Outcomes of Pharmacogenomic Testing Among Children and Adolescents in Outpatient Psychiatric Treatment: A Quality Improvement Project

A Scholarly Project Presented to the Faculty of the Nicole Wertheim College of Nursing and Health Sciences

Florida International University

In partial fulfillment of the requirements
For the Degree of Doctor of Nursing Practice

By

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Approval Acknowledged: DocuSigned by: _____, DNP Program Director
Date: 7/25/2024

Abstract

Psychiatric disorders in children and adolescents have multifactorial etiologies encompassing genetic and environmental factors. The increasing incidence of mental health issues in this population, exacerbated by the COVID-19 pandemic, has highlighted the need for more precise treatment strategies. Pharmacogenomic (PGx) testing, which tailors medication selection based on genetic profiles, offers a promising approach to improving psychiatric care. Despite the potential benefits of PGx testing, its application in child and adolescent psychiatry remains limited due to insufficient high-quality evidence. This study aims to evaluate the clinical outcomes of PGx testing in a pediatric population at an outpatient mental health practice in Miami, Florida. This quality improvement (QI) project involved a retrospective chart review of 10 pediatric patients aged 7-17 who underwent PGx testing. Data were collected on demographics, psychiatric and medical comorbidities, genetic variants, and clinical outcomes measured using the Clinical Global Impressions (CGI) Scale. Descriptive statistics, distribution, correlation, and regression analyses were conducted to assess the relationships between genetic variants, medication trials, side effects, and treatment responses. The sample included predominantly Caucasian/Hispanic adolescents with an average age of 13.6 years. ADHD was the most common primary diagnosis. PGx tests utilized included Genomind, Genesight, Tempus, and Toolbox, with Genomind being the most frequently used. Notably, 50% of patients exhibited marked improvement in medication response, and 40% showed moderate improvement. The analysis indicated a weak positive correlation between the number of medication trials and CGI-I scores, suggesting that more trials were associated with slightly worse treatment responses. Regression analysis revealed that genetic variants and the number of medication trials did not significantly predict treatment response, highlighting the need for larger sample sizes. The

findings suggest that PGx testing can enhance treatment efficacy by tailoring medication choices based on individual genetic profiles. PGx testing shows promise in improving the precision of psychopharmacological treatment in children and adolescents, potentially reducing the trial-and-error process of medication adjustments. Integrating PGx testing into clinical practice could enhance treatment outcomes, adherence, and overall quality of life for pediatric patients with psychiatric disorders. Further research is necessary to establish its broader clinical utility and cost-effectiveness.

Keywords: pharmacogenomic testing, child and adolescent psychiatry, psychiatric disorders, genetic variants, personalized medicine

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Introduction

Problem Statement

Psychiatric disorders are known to arise from complex etiologies of biological and environmental factors. Large-scale genomic studies show that genetic variations substantiate a significant risk of developing psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and attention-deficit hyperactivity disorder (Smoller et al., 2018). A growing understanding of the genetic architecture underlying psychopathology generates promising new ideas about diagnostic and treatment practices within psychiatry (Sullivan & Geschwind, 2019). Currently, pharmacogenomic testing exists as a resource that aims to shorten the often lengthy trial-and-error process of psychopharmacological management by guiding medication selection and dosing based on an individual's genetic information (Bousman et al., 2021).

Mental health problems among children and adolescents have increased remarkably over the past few decades, with a sharp acceleration due to the COVID-19 pandemic (Bommersbach et al., 2023). Pediatric patients commonly experience multiple medication trials before identifying a sufficiently tolerated medication that successfully treats symptoms (Wehry et al., 2018). This approach frequently leads to a further reduction in quality of life. The American Academy of Child and Adolescent Psychiatry (AACAP) recommends that clinicians avoid using pharmacogenomic (PGx) testing to select psychotropic medications in children and adolescents until further high-quality research assesses its clinical significance (2020). This project seeks to contribute to the conversation about the possible value of PGx testing in child and adolescent psychiatry.

Significance

Genetic makeup determines much of an individual's response to a medication. Pharmacogenomic testing mainly evaluates genetic variations relevant to medication metabolism to predict treatment efficacy (Wehry et al., 2018). Pharmacokinetics describes the process of a drug's movement through the body. Variants of genes encoding drug-metabolizing enzymes and drug transporters impact enzymatic activity and drug distribution, thereby modifying the pharmacokinetic profile of a medication (Bousman et al., 2021). Most psychotropic medications undergo hepatic metabolism. For this reason, the cytochrome P450 (CYP) enzyme system is considered the most clinically significant for psychotropic drug metabolism (Bousman et al., 2021). CYP genotypes translate to metabolizer phenotypes, describing the predicted metabolic capacity of an individual's genetics: poor metabolizer, intermediate metabolizer, normal metabolizer, rapid metabolizer, and ultrarapid metabolizer (Caudle et al., 2017). These phenotypes correlate to the estimated tolerance and efficacy of specific antidepressants, antipsychotics, anxiolytics, and other psychotropic medications (Bousman et al., 2021).

Additionally, pharmacogenomic testing assesses methylenetetrahydrofolate reductase (MTHFR) gene variations. The MTHFR enzyme is essential in producing methylfolate and ultimately developing the monoamine neurotransmitters associated with mood regulation (Farah, 2009). Decreased MTHFR enzyme activity due to a gene variation impacts neurotransmitter production, affecting mood. Two prominent MTHFR variations significantly link to schizophrenia, bipolar disorder, and major depressive disorder (Zhang et al., 2022). Individuals with MTHFR variations may benefit from adjunctive L-methylfolate (Farah, 2009). Implementing pharmacogenomic testing to identify MTHFR variations can lead to effective alternative therapies (Gardner et al., 2014).

Scope and Consequences of the Problem

Psychiatric disorders are a leading cause of disability among children and adolescents worldwide (Erskine et al., 2014). In the United States, the mental health of its young people has become an emergency. From 2009 to 2019, suicide rates among Americans ages 10 to 24 increased by 57% (Curtin, 2020). One in five children younger than 18 in the United States experiences a psychiatric disorder yearly (Whitney & Peterson, 2019). One in four children received mental health services in 2022 (Bitsko et al., 2022). Still, the national prevalence of children with a psychiatric disorder who do not receive the required treatment is 49.4% (Whitney & Peterson, 2019). The burden on young people and their families is overwhelming.

Mental health problems that begin in childhood may yield consequences that last a lifetime. Many children and adolescents who experience psychiatric illness tend to exhibit impaired mental health, decreased satisfaction with life, and lower health-related quality of life in adulthood (Schlack et al., 2021). Individuals with a childhood psychiatric disorder have a six times greater chance of at least one adverse health, legal, financial, or social outcome as an adult than those without a history of childhood mental health problems (Copeland et al., 2015). Early intervention and effective treatment at the onset of psychiatric illness are integral to an individual's well-being across the lifespan (Colizzi et al., 2020). Pharmacogenomic testing has the potential to aid significantly in the treatment process of children and adolescents with psychiatric disorders who require medication. Integrating genetic information into decision-making can reduce morbidity, lessen side effects, improve treatment response, decrease hospitalizations, and lower care costs for patients and families (Wehry et al., 2018).

Knowledge Gaps

Due to knowledge gaps, pharmacogenomic testing has yet to be widely used among pediatric or adult patients. In 2018, the FDA stated that there was insufficient evidence to defend the relationship between genetic variations and antidepressant medications, advising patients not to modify their treatment based on the results of a pharmacogenomic test (Kastrinos et al., 2020). While significant evidence now demonstrates its efficacy in adults with depression (Arnone et al., 2023; Bousman et al., 2017; Tiwari et al., 2022), further double-blinded randomized controlled trials are warranted among varying populations. Very few studies involve children or adolescents. To date, only one randomized controlled trial has investigated pharmacogenetic testing in adolescent depression, which showed no statistical difference between those who received pharmacogenomic testing and those who did not (Vande Voort et al., 2022). Retrospective studies involving children and adolescents with depression and anxiety demonstrate notable improvements in clinical outcomes as measured by the Clinical Global Impressions Scale (Blasco-Fontecilla, 2016; Dagar et al., 2022). More robust investigation is required to determine the clinical significance of pharmacogenomic testing in pediatric populations.

Knowledge among patients and providers regarding pharmacogenomic testing is limited. Despite the low familiarity with the concept, patients declare a strong interest in participating (Kastrinos et al., 2020). More patients report learning about pharmacogenomic testing from a source outside the healthcare system than from their psychiatrist, nurse practitioner, or primary care provider (Kastrinos et al., 2020). In a survey of physicians and pharmacists practicing psychiatry, 81% of participants believed that pharmacogenomic testing would help identify appropriate treatment; however, only 46.4% felt capable of ordering these tests (Chan et al.,

2017). Pharmacogenomics education in medical, pharmacy, and nursing schools has improved considerably over the past ten years (Green et al., 2010; Kuželički et al., 2019), but instruction in graduate nursing coursework continues to be an area of needed progress (Kaltenreider et al., 2023).

Proposal Solution

Barriers to widespread utilization of pharmacogenomic testing persist despite awareness and understanding of their resolutions. The most commonly cited barriers are evidence for the clinical utility of pharmacogenomic testing, its cost-effectiveness, and provider knowledge (Virelli et al., 2021). Evidence for the clinical significance of pharmacogenomic testing requires further research across varying patient populations, especially among child and adolescent populations and at the highest hierarchical level (Gardner et al., 2014). Due to the costly nature of randomized controlled trials, authorship of most to date includes individuals with biased interest in the success of pharmacogenomic testing, which jeopardizes the reliability and generalizability of available evidence (Virelli et al., 2021). Uninvolved exploration into the topic, as this project aims to provide, is invaluable. With numerous commercial and noncommercial pharmacogenomic tests available on the market, comparing and overall determination of cost-effectiveness is challenging. Geographical context is also meaningful (Virelli et al., 2021). This project presents the opportunity to analyze multiple pharmacogenomic testing products in a culturally and economically diverse setting in South Florida. Lastly, this project targets provider knowledge to disseminate analysis and stimulate discussion among the advanced practice nursing community.

Summary of the Literature

Mental health problems among children and adolescents in the United States are at an all-time high. One in five American children experiences mental illness (Bitsko et al., 2022). Pediatric mental health- and suicide-related emergency department visits have increased exponentially in the past few years (Bommersbach et al., 2023). For young patients who require pharmacological intervention, a trial-and-error process of multiple medications is common before determining an effective treatment approach (Wehry et al., 2018). Pharmacogenomic (PGx) testing is a clinical decision-support tool that guides medication selection and dosing based on genetic information, potentially decreasing the number of unsuccessful medication trials for patients (Bousman et al., 2021). Currently, the American Academy of Child and Adolescent Psychiatry (AACAP) recommends that clinicians avoid PGx testing in children and adolescents until further high-quality research assesses its clinical significance (2020). This literature review seeks to summarize the existing knowledge regarding the use of PGx testing in child and adolescent psychiatry.

Search Strategy of the Literature

Online electronic journal databases searched included CINAHL, CINAHL Plus with Full Text, Health Source: Nursing/Academic Edition, Academic Search Complete, and Google Scholar. Findings were restricted based on the following limits: full-text, peer-reviewed, academic journal, published between 1990 and 2024, and sorted by relevance. Due to limited research within the past ten years alone, the extensive timeframe allowed for more robust results. Searches were conducted with the following terms: "pharmacogenomic testing" or

"pharmacogenomics" or "genetic testing" and "child" or "children" or "adolescent" or "pediatric" and "psychiatry" or "psychiatric" or "mental health." Searches yielded 40 relevant articles.

Advanced Literature Review

Basics of PGx Testing

PGx testing evaluates genetic variations related to medication metabolism and drug targets to indicate treatment response (Wehry et al., 2018). This testing ideally maximizes the likelihood that a specific medication will be effective with minimal adverse outcomes. The first FDA-approved pharmacogenomic test, the AmpliChip CYP450, focused on single gene variations in the cytochrome P450 (CYP450) system. Newer tests utilize algorithms to assess the CYP450 system in combination with pharmacodynamic genes related to the mechanisms of action of various medications to determine a unique profile that may guide medication selection and dosing for several classes of psychotropic drugs (Wehry et al., 2018).

CYP450 Enzymes

The CYP450 system refers to a group of enzymes essential to eliminating many medications (Wehry et al., 2018). Most CYP450 enzymes are expressed in the liver, which serves as the primary site of drug metabolism. These enzymes represent Phase 1 metabolism, in which they convert lipid-soluble drugs to water-soluble compounds for excretion through the kidneys. Multiple alleles exist for each enzyme, resulting in highly variable enzymatic activity. Alleles may code for normal function, enhanced function, or decreased to no function. Based on metabolic phenotype, individuals are classified as normal, poor, intermediate, and ultrarapid metabolizers (Kalman et al., 2016). An individual who is a poor metabolizer of a specific

CYP450 enzyme may require decreased doses of a medication metabolized through that system to avoid adverse effects. Conversely, an individual who is an ultrarapid metabolizer may require larger doses to achieve therapeutic effects.

CYP450 enzymes significantly involved in psychotropic medication metabolism include CYP2D6, CYP2C19, CYP1A2, and CYP3A4 (Wehry et al., 2018). The CYP2D6 system is the primary metabolizer for over 70 medications, including many selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants such as fluoxetine, paroxetine, venlafaxine, atomoxetine, and amitriptyline (Spina et al., 2003). Some medications, like fluoxetine and paroxetine, are metabolized by CYP2D6 and inhibit the CYP2D6 system. Therefore, individuals who are normal CYP2D6 metabolizers can become poor metabolizers following the administration of certain drugs. The CYP2C19 system is the primary metabolizer for over 50 medications, including citalopram and escitalopram (Wehry et al., 2018). Poor CYP2C19 metabolizer phenotypes are notable among Asian populations (Poolsup et al., 2000), while about one-third of Caucasian individuals are ultrarapid metabolizers (Chang et al., 2014). The CYP1A2 system is the primary metabolizer for fluvoxamine (Mrazek, 2010) and duloxetine, the only SNRI approved for use in pediatric patients (Strawn & Delbello, 2008). The CYP3A4 system metabolizes over 50% of all medications (Wehry et al., 2018). While CYP3A4 gene expression is highly variable, few genetic variants are associated with enzyme activity (Lamba et al., 2014). Medications, diet, and other environmental factors can influence gene expression.

In addition to genetic variants, medication metabolism via CYP450 systems is impacted by development (Kearns et al., 2003). CYP2C19 activity reaches the adult range by age six months, peaks at 1.5-1.8 times higher than the adult range by age 3-4 years, and returns to the

adult range by the end of puberty. CYP3A4 activity reaches the adult range by age 6-12 months, peaks above the adult range from ages 1-4, and returns to the adult range by the end of puberty. CYP1A2 activity reaches the adult range by age four months, peaks above the adult range at age 1-2 years, and returns to the adult range by the end of puberty. CYP2D6 activity reaches and remains at the adult range by age 3-5 (Leeder & Kearns, 1997).

Pharmacodynamic Genes

Pharmacodynamic factors determine how a medication interacts with its molecular target to achieve its mechanism of action (Wehry et al., 2018). Variations in genes relevant to the mechanisms of action of psychotropic medications may affect treatment response. Significant pharmacodynamic genes include SLC6A4, HTR2A, and COMT. The SLC6A4 gene encodes the presynaptic serotonin transporter, which is responsible for the return of synaptic serotonin to the presynaptic terminal. SSRIs block this transporter to exert therapeutic effects. Variants of this gene result in altered expression of the transporter, which may impact SSRI efficacy (Serretti et al., 2007). The HTR2A gene encodes the serotonin receptor responsible for postsynaptic serotonin signaling, a significant target for antidepressant and antipsychotic medications (Smith et al., 2013). Research suggests that the HTR2A gene and genetic variations influence the response to antidepressants (Kirchheiner et al., 2004; Lucae et al., 2010). Catechol-o-methyltransferase (COMT) is the enzyme responsible for the inactivation of catecholamines such as norepinephrine and dopamine, which are implicated in ADHD and serve as targets for stimulants (Wehry et al., 2018). An identified COMT gene variation results in a 40% reduction of enzymatic activity, leading to higher levels of circulating catecholamines in the brain (Lachman et al., 1996). This variation is associated with a decreased response to methylphenidate (Froehlich et al., 2011; Mills et al., 2004).

Support for Implementation of PGx Testing in Children and Adolescents

Examples of research supporting the utilization of PGx testing among children and adolescents involve non-psychotropic and psychotropic medications from infancy onward.

Codeine

A prominent example of research supporting the use of PGx testing in children concerns the gene-drug interaction between CYP2D6 and codeine (Tang Girdwood et al., 2022). The CYP2D6 system metabolizes codeine to its active metabolite, morphine (Thorn et al., 2009). In vitro studies demonstrate variable morphine production based on CYP2D6 genotypes (Shen et al., 2007; Yu et al., 2002; Zhang et al., 2009). CYP2D6 ultrarapid metabolizers have higher morphine production than normal metabolizers, while poor metabolizers have lower morphine production (Gaedigk et al., 2017). Morphine has a very high affinity for opioid receptors with the potential to cause respiratory depression and death (Thorn et al., 2009). Low morphine production may lead to inadequate pain control.

Reports of severe adverse drug events (ADEs) in infants of breastfeeding mothers who were taking codeine led to the discovery that high morphine concentrations in some symptomatic infants were related to CYP2D6 ultrarapid metabolizer phenotypes (Madadi et al., 2007). As a result, the FDA recommended caution when prescribing codeine to breastfeeding mothers who are CYP2D6 ultrarapid metabolizers. In 2009, a toddler, later determined to be a CYP2D6 ultrarapid metabolizer, died after taking codeine after an uncomplicated adenotonsillectomy (Ciszkowski et al., 2009). Following a review of ADEs reported in children taking codeine after tonsillectomy and adenoidectomy procedures and with altered CYP2D6 metabolism, the FDA issued a new warning stating the contraindication of codeine in children following tonsillectomy

and adenoidectomy procedures (FDA, 2013). In 2014, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines strongly advised against the use of codeine in ultrarapid metabolizers due to the potential for toxicity and in poor metabolizers due to lack of efficacy (Crews et al., 2014). In 2017, the FDA added a contraindication for codeine to treat cough or pain in children under age 12 (FDA, 2019). Some argue that pharmacogenomic testing could enable the safe use of codeine in children (Gammal et al., 2019).

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are the most prescribed antidepressant class among pediatric and adolescent patients (Olfson et al., 2013). SSRIs block presynaptic serotonin reuptake to increase serotonergic activity (Lochmann & Richardson, 2019). FDA-approved indications for some SSRIs in pediatric and adolescent patients include depression and obsessive-compulsive disorder (Aka et al., 2017). Other SSRIs are used off-label for anxiety and stress disorders. Common ADEs associated with SSRI use in children and adolescents are gastrointestinal upset, activation, and sleep disturbance (Rossow et al., 2020).

In vitro studies show the relationship between CYP variants and SSRI concentrations (Hicks et al., 2015). CYP2C19 extensively metabolizes sertraline, citalopram, and escitalopram. CYP2D6 extensively metabolizes paroxetine and fluvoxamine. Both CYP2C19 and CYP2D6 significantly metabolize fluoxetine. Poor CYP metabolizers have higher SSRI concentrations than normal, rapid, or ultrarapid metabolizers (Chang et al., 2014). Based on the CYP2C19 metabolizer phenotype for sertraline, citalopram, and escitalopram, and the CYP2D6 metabolizer phenotype for paroxetine and fluvoxamine, CPIC guidelines suggest reducing the initial dosage

or seeking an alternative option in poor metabolizers to avoid ADEs and seeking an alternative option in ultrarapid metabolizers to avoid inadequate treatment (Hicks et al., 2015).

Evidence for pharmacogenomic influence varies among SSRIs within child and adolescent populations (Tang Girdwood et al., 2022). Studies investigating escitalopram and citalopram indicated that CYP2C19 ultrarapid metabolizers had a slower escitalopram dose increase over time (Bishop et al., 2015), while poor and intermediate metabolizers had higher escitalopram/citalopram plasma levels (Rudberg et al., 2006). The most extensive and recent study of CYP2C19 effects on antidepressant response in children and adolescents demonstrated a higher rate of discontinuation of escitalopram/citalopram in poor metabolizers compared to other metabolizers due to ADEs (Aldrich et al., 2019). Poor metabolizers reported the most side effects, including activation and weight gain. Rapid and ultrarapid metabolizers reported the fewest side effects and experienced faster treatment response. Three studies investigating sertraline found no relationship between CYP2C19 function and treatment response in pediatric patients (Aldrich et al., 2019; AlOlaby et al., 2017; Poweleit et al., 2019), while another study demonstrated that children with reduced CYP2C19 metabolism had fewer ADEs (Rossow et al., 2020). Studies investigating CYP2D6 function and fluoxetine treatment response in pediatric patients did not indicate effects on clinical outcomes (Ramsey et al., 2019; Troy et al., 2020). Additionally, four pediatric studies link variations in the SLC6A4 gene to SSRI treatment response and ADEs (Kronenberg et al., 2007; Owley et al., 2009; Rotberg et al., 2013; Sugie et al., 2005).

Attention-Deficit Hyperactivity Disorder Medications

Attention-deficit hyperactivity disorder (ADHD), a common diagnosis among children and adolescents, is treated with stimulant and non-stimulant medications (Bruxel et al., 2019; Wolraich et al., 2019). Methylphenidate- and amphetamine-based stimulants and non-stimulants, including atomoxetine, guanfacine, and clonidine, are FDA-approved to treat ADHD in children ages six and older. Variations in the COMT enzyme responsible for inactivating dopamine and norepinephrine are associated with decreased enzyme activity (Lachman et al., 1996) and decreased stimulant response (Cheon et al., 2008; Kereszturi et al., 2008). Despite this evidence, treatment adjustments are not currently recommended based on COMT gene variations. While CYP450 enzymes do not significantly metabolize methylphenidate, some amphetamine medications, such as dextroamphetamine, are metabolized by CYP2D6 (Feder et al., 2018). There is no pediatric or adult data suggesting amphetamine dosing based on CYP2D6 genotypes at this time (Tang Girdwood et al., 2022). Atomoxetine, a selective norepinephrine reuptake inhibitor, is primarily metabolized by CYP2D6 (Brown et al., 2019). Pediatric research indicates that CYP2D6 poor metabolizers taking atomoxetine had a better treatment response but also experienced more ADEs (Brown et al., 2019; Trzepacz et al., 2008). The FDA and CPIC recommend atomoxetine dosing adjustments based on CYP2D6 genotypes (Brown et al., 2019).

Actionable Gene-Drug Pairs

A retrospective review investigated the use of PGx testing among 452 pediatric patients to assess its value in this population and determine targets for future research (Roberts et al., 2021). Test results were reviewed to identify genetic variants with evidence-based guidance for medication management to define actionable gene-drug pairs. The study identified 78 actionable gene-drug pairs associated with the 28 genes tested in 98.7% of patients. Gene-drug-diagnosis groups were defined by incorporating clinical diagnoses for which medication guidance could be

utilized. The study identified 203 gene-drug-diagnosis groups. Of the patients with an actionable gene-drug-diagnosis group, 49.3% had a diagnosis that correlated with the drug as a therapeutic option, allowing PGx-guided treatment selection. Of the patients with an associated diagnosis, 30.9% had a prescription for the actionable drug, qualifying PGx-guided dosing. The most common gene-drug-diagnosis groups with matching diagnoses and prescriptions were CYP2C19-citalopram-escitalopram-depression in 3.3% of patients, CYP2C19-dexlansoprazole-gastritis-esophagitis in 3.1% of patients, CYP2C19-omeprazole-gastritis-esophagitis in 2.4% of patients, CYP2D6-atomoxetine-attention deficit hyperactivity disorder in 2.2% of patients, and CYP2C19-citalopram-escitalopram-obsessive-compulsive disorder in 1.5% of patients. The results indicated that PGx could guide treatment in nearly half (48.7%) of the pediatric patients tested, and mood disorders are favorable targets for future research in PGx testing because of the high prevalence of these diagnoses and corresponding actionable gene-drug pairs identified in the population.

Risks and Benefits of PGx Testing

Of the hundreds of drugs included on the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, over half are approved for use in children and adolescents (FDA, 2019). However, most data on PGx testing are collected on adults (Haga, 2019). Findings in adults may not extend to children and adolescents (Maruf et al., 2019). Furthermore, the interpretation of existing pediatric data may be challenging due to developmental changes that impact pharmacokinetics (Leeder & Kearns, 2012). Therefore, the most significant risk is the challenge to determine the clinical significance of treatment response or ADE risk in pediatric populations. Additional considerations include the stress of sample collection for children and the risk of psychological harm from learning PGx testing results (Haga, 2019). Most tests require minimally

invasive buccal swabs or saliva samples, but some involve blood draws (Ramsey et al., 2019). Children and their parents may experience feelings of anxiety or fear if their child is determined to have a severe phenotype or a genetic variation that significantly limits treatment options (Haga, 2019). Strengthened apprehension may lead to poor medication adherence. Alternatively, children and their parents may benefit from reduced anxiety and fear regarding treatment efficacy and ADEs based on favorable test results, leading to increased medication compliance and improved likelihood of positive clinical outcomes (Haga, 2019).

Purpose

The purpose of this quality improvement (QI) project was to increase the knowledge of pharmacogenomic testing in child and adolescent psychiatry based on clinical outcomes in an outpatient private mental health practice in Miami, Florida.

PICO

The PICO question investigated the following:

Population (P): Child and adolescent patients in outpatient private mental health practice

Intervention (I): Pharmacogenomic testing and corresponding recommended treatment

Comparison (C): None

Outcomes (O): Improved medication response and treatment outcomes

Definition of Terms

PGx test = a clinical decision-support tool that guides medication selection and dosing based on genetic information evaluating pharmacokinetic and pharmacodynamic genes. Most tests require

minimally invasive buccal swabs or saliva samples. Commercially available tests include Genomind, Genesight, Tempus, and Toolbox.

Pharmacokinetics = the process of a drug's movement through the body.

CYP450 system = the system through which the majority of psychotropic medications undergo hepatic metabolism. Multiple alleles exist for each CYP enzyme, resulting in highly variable enzymatic activity. Alleles may code for normal function, enhanced function, or decreased to no function.

Metabolizer phenotype = the classification assigned based on the function of a specific genetic variant (allele) that indicates how well the body processes drugs through a specific metabolic pathway. Individuals are classified as normal, poor, intermediate, and ultrarapid metabolizers

Poor metabolizer = an individual who processes medication very slowly through the specified pathway, potentially requiring decreased doses to avoid side effects because the medication stays in their system longer.

Intermediate metabolizer = an individual who processes medication at a slower rate than normal but faster than a poor metabolizer, potentially requiring dose adjustment.

Normal (extensive) metabolizer = an individual who processes medication at the expected normal rate and usually requires standard dosing.

Rapid metabolizer = an individual who processes medication faster than normal, potentially requiring dose adjustment to achieve the desired effect because the medication does not stay in their system as long.

Ultrarapid metabolizer = an individual who processes medication very quickly, even faster than a rapid metabolizer, potentially requiring a significantly higher dose or different medication to ensure the treatment is effective, as the standard dose might not work well.

Pharmacodynamics = how a medication interacts with its molecular target to achieve its mechanism of action. Variations in genes relevant to the mechanisms of action of psychotropic medications may affect treatment response. Significant pharmacodynamic genes include SLC6A4, HTR2A, and COMT.

SLC6A4 gene = encodes the presynaptic serotonin transporter, which is responsible for the return of synaptic serotonin to the presynaptic terminal. SSRIs block this transporter to exert therapeutic effects. Variants of this gene result in altered expression of the transporter, which may impact SSRI efficacy.

HTR2A gene = encodes the serotonin receptor responsible for postsynaptic serotonin signaling, a significant target for antidepressant and antipsychotic medications. This gene influences the response to antidepressants.

COMT gene = encodes catechol-o-methyltransferase (COMT), the enzyme responsible for inactivating catecholamines such as norepinephrine and dopamine. These catecholamines are implicated in ADHD and serve as targets for stimulants. This gene influences the response to stimulants.

MTHFR gene = encodes methylenetetrahydrofolate reductase (MTHFR), the enzyme essential in producing methylfolate and ultimately developing the monoamine neurotransmitters associated with mood regulation. Decreased MTHFR enzyme activity due to a gene variation

impacts neurotransmitter production and links significantly to schizophrenia, bipolar disorder, and major depressive disorder. Individuals with MTHFR variations may benefit from adjunctive L-methylfolate.

Theoretical Framework

Katherine Kolcaba's "Theory of Comfort" (1994, 2003) is a framework for this project. This theory aligns with the restorative goals of PGx-guided treatment and the principles of pediatric nursing. Children and adolescents are among the most vulnerable patients in the healthcare system (Waisel, 2013). Young patients and their families require significant support in navigating the challenges of seeking treatment. Fear and anxiety may surface for patients and parents alike when encountering unfamiliar diagnostic procedures and therapeutic practices. PGx testing is a tool that aims to guide and enhance the mental health treatment process, alleviating discomfort.

The fundamental concepts of the "Theory of Comfort" are that "a) human beings have holistic responses to complex stimuli; b) comfort is a desirable outcome that is germane to the discipline of nursing; and c) human beings strive to meet, or have met, their basic comfort needs" (Kolcaba, 1994, p. 1178). Kolcaba defines comfort as a "state of being strengthened" (2003, p. 251). Comfort comprises two dimensions (Kolcaba, 1994). The first dimension involves three states: relief, ease, and transcendence. The second dimension describes the contexts in which comfort occurs: physical, psychospiritual, social, financial, and environmental. This multifaceted understanding of comfort mirrors the holistic approach to pediatric nursing, which addresses the developmental, physical, emotional, mental, spiritual, and genetic factors of each young patient and their family (Kolcaba & DiMarco, 2005).

Methodology

Setting

This QI project was conducted at an outpatient private mental health practice in Miami, Florida.

Sample/Participants

This study included pediatric patients who completed pharmacogenomic testing as part of their psychiatric treatment plan. Participants were identified by two psychiatric mental health nurse practitioners who provided. The sample size consisted of 10 pediatric patients.

Project Design

This QI project employed a retrospective chart review of PGx testing of pediatric patients. Patients were eligible for inclusion in the study if they received care at the outpatient private mental health practice between January 1, 2020, and April 1, 2024, were aged 7-17, and completed PGx testing.

Protection of Human Subjects

This QI project evaluated deidentified and completely anonymous secondary data provided by the outpatient private mental health practice. Stringent data deidentification processes were implemented to remove and code all personal identifiers before analysis, ensuring that data cannot be traced back to individual patients. The investigator did not access organizational records or protected health information. The investigator utilized secure, encrypted databases for storing deidentified data.

Data Collection

Treating psychiatric mental health practitioners at the outpatient private mental health practice identified suitable participants and provided deidentified data, including patient age, sex, race/ethnicity, psychiatric and medical comorbidities, treatment history, and genetic variants. Based on the CPIC guidelines, patients were identified as poor, intermediate, rapid, and ultrarapid metabolizers (Caudle et al., 2017). The psychiatric mental health nurse practitioners measured clinical outcomes using the Clinical Global Impressions (CGI) Scale (Busner & Targum, 2007). The CGI is a validated research rating tool that considers all available data, including the patient's history, symptoms, and the impact of the symptoms on the patient's functioning. The CGI-Improvement component rates change from the start of treatment in a single query rated on a seven-point scale.

Data Analysis/Management

Data was cleaned and organized by the investigator for analysis. Data analysis included descriptive statistics, distribution analysis to investigate the distribution of key variables in the dataset, correlation analysis to investigate relationships between genetic variants and treatment responses/side effects, and regression analysis to determine significant predictors of marked treatment response and the presence of side effects.

Nursing Practice Dissemination

Findings from the study were presented at Florida International University's DNP Symposium and to the outpatient private mental health practice involved. The research will be

submitted to the Journal of the American Psychiatric Nurses Association for possible publication.

Results

Demographics

Data from 10 patients were analyzed, including variables such as age, sex, and race/ethnicity. Patients ranged from 10 to 17 years old, with an average age of 13.6. The cohort included four females and six males. The majority of patients were Caucasian/Hispanic. Three patients were also identified as Jewish.

Psychiatric Conditions and Medical Comorbidities

The most common primary diagnosis was ADHD (ICD-10: F90.2), present in 50% of the patients (5 out of 10). Comorbid conditions included anxiety disorders, depressive disorders, OCD, and bipolar disorder. Two patients had significant medical comorbidities requiring medication.

PGx Testing

PGx tests used included Genomind, Tempus, Toolbox, and Genesight. Genomind was the most commonly used test. Genetic variants analyzed included CYP2D6, CYP2C19, SLC6A4, BDNF, MTHFR, ADRA2A, COMT, and others.

Medication Response and Side Effects

Marked improvement was noted in the overall medication response in 50% of patients (5 out of 10). Moderate improvement was observed in 40% of patients (4 out of 10). Minimal

improvement was seen in 10% of patients (1 out of 10). Side effects were reported in 40% of patients (4 out of 10). The most common side effect was increased anxiety related to Concerta (extended release methylphenidate). Other side effects included decreased appetite, upset stomach, diarrhea, emotional lability, and worsening of OCD symptoms.

Distribution Analysis

Distribution of CGI-I Scores

The majority of patients had CGI-I scores indicating significant improvement (CGI-I score 1). See Figure 1.

Distribution of Number of Medication Trials

Most patients underwent multiple medication trials before achieving an optimal response. See Figure 2.

Correlation Analysis

A correlation analysis was performed on the dataset to determine the strength and direction of the relationships between variables, such as the number of medication trials, treatment response, side effects, and genetic variants. These insights allow for improved understanding of how genetic variants might influence medication efficacy and side effects, which may inform personalized treatment strategies.. Relevant numerical variables were selected for correlation analysis, including the number of medication trials, overall pharmacological treatment response (quantified), CGI-I score, and presence of specific genetic variants (binary coded: 1 for presence, 0 for absence). The Pearson correlation coefficient was used to quantify

the relationships between these variables. The resulting correlation matrix was analyzed to identify significant correlations. All correlations indicated weak relationships without statistical significance.

Medication Trials and CGI-I Scores

A weak positive correlation ($r = 0.200$) was found between the number of medication trials and CGI-I scores. This indicates that as the number of medication trials increases, the CGI-I scores tend to increase slightly, suggesting a worse treatment response. This correlation is not statistically significant ($p = 0.580$). See Figure 3.

Medication Trials and Response

A weak positive correlation ($r = 0.183$) exists between the number of medication trials and the overall pharmacological treatment response. This indicates that as the number of medication trials increases, the treatment response tends to slightly increase, suggesting a worse treatment response. This correlation is not statistically significant ($p = 0. 613$). See Figure 4.

Genetic Variants and Side Effects

A weak negative correlation ($r = -0.218$) exists between the SLC6A4 L(A)/S genetic variant and gastrointestinal side effects, suggesting this genetic variant is slightly associated with fewer GI side effects. This correlation is not statistically significant ($p = 0.545$). A weak negative correlation ($r = -0.272$) exists between the BDNF Val/Met genetic variant and anxiety symptoms, suggesting this genetic variant is slightly associated with fewer anxiety symptoms. This correlation is not statistically significant ($p = 0.447$).

Regression Analysis

A regression analysis was performed to predict treatment response based on genetic variants and the number of medication trials based on the hypothesis that genetic predispositions and previous treatment attempts would influence the efficacy of prescribed medications. Treatment response was quantified on a numerical scale where higher values represent better outcomes (e.g., marked, moderate, minimal improvement). Genetic variants included specific markers such as CYP2B6, CYP3A5, CYP2C19, BDNF, and MTHFR, which were hypothesized to affect drug metabolism and response. The number of medication trials was a continuous variable representing how many medications a patient had tried before reaching the current assessment point. Given the small sample size, a simplified regression model was used. The R-squared value of 0.451 indicates that the selected features can explain approximately 45.1% of the variability in the treatment response. However, the negative adjusted R-squared suggests that the model may not fit best given the small sample size and complexity. The intercept is statistically significant with a p-value of 0.011, indicating a baseline treatment response level when all predictors are zero. None of the selected genetic variants are statistically significant predictors at the 5% significance level (all p-values > 0.05). The simplified regression model indicated that the selected genetic variants and the number of medication trials did not significantly predict the treatment response in this small sample of patients, but the intercept remains significant. The results suggest that a larger sample size or additional relevant predictors may be needed to better understand the relationships and make accurate predictions.

Analysis of MTHFR Variant

Within this sample, 50% of the patients (5 out of 10) were determined to have MTHFR genetic variants associated with reduced activity. Of the patients with MTHFR variants, 80% (4 out of 5) were prescribed supplemental L-methylfolate. The average CGI-I score of these patients prescribed L-methylfolate was 2.0. The average CGI-I score of these patients not prescribed L-methylfolate was 2.0. The average pharmacological treatment response of these patients prescribed L-methylfolate was 1.5 (between "marked" and "moderate"), while the average pharmacological treatment response of these patients not prescribed L-methylfolate was 2.0 ("moderate"). The average CGI-I score is equal for both groups (2.0), indicating that, on average, both groups had a "much improved" treatment response. Patients with the MTHFR variant who were prescribed L-methylfolate had a slightly better average treatment response (1.5) than those who were not prescribed L-methylfolate (2.0). The analysis suggests that prescribing L-methylfolate to patients with the MTHFR variant may be associated with a slightly better overall medication treatment response. However, the small sample size (only five patients) limits the statistical power and generalizability of these findings.

Half of the patients did not have an MTHFR variant (5 out of 10). None of these patients was prescribed supplemental L-methylfolate. The average CGI-I score of patients without the MTHFR variant was 1.75. The average pharmacological treatment response of these patients was 1.75 (between "marked" and "moderate"). Patients without the MTHFR variant who were not prescribed L-methylfolate had a slightly better average CGI-I score (1.75) compared to those with the MTHFR variant (2.0), regardless of L-methylfolate prescription. See Figure 5. Overall, patients with the MTHFR variant prescribed L-methylfolate show the best treatment response, followed by non-MTHFR patients not prescribed L-methylfolate, and lastly, MTHFR patients not prescribed L-methylfolate. See Figure 6.

Graphs

Figure 1.

Distribution of CGI-I Scores

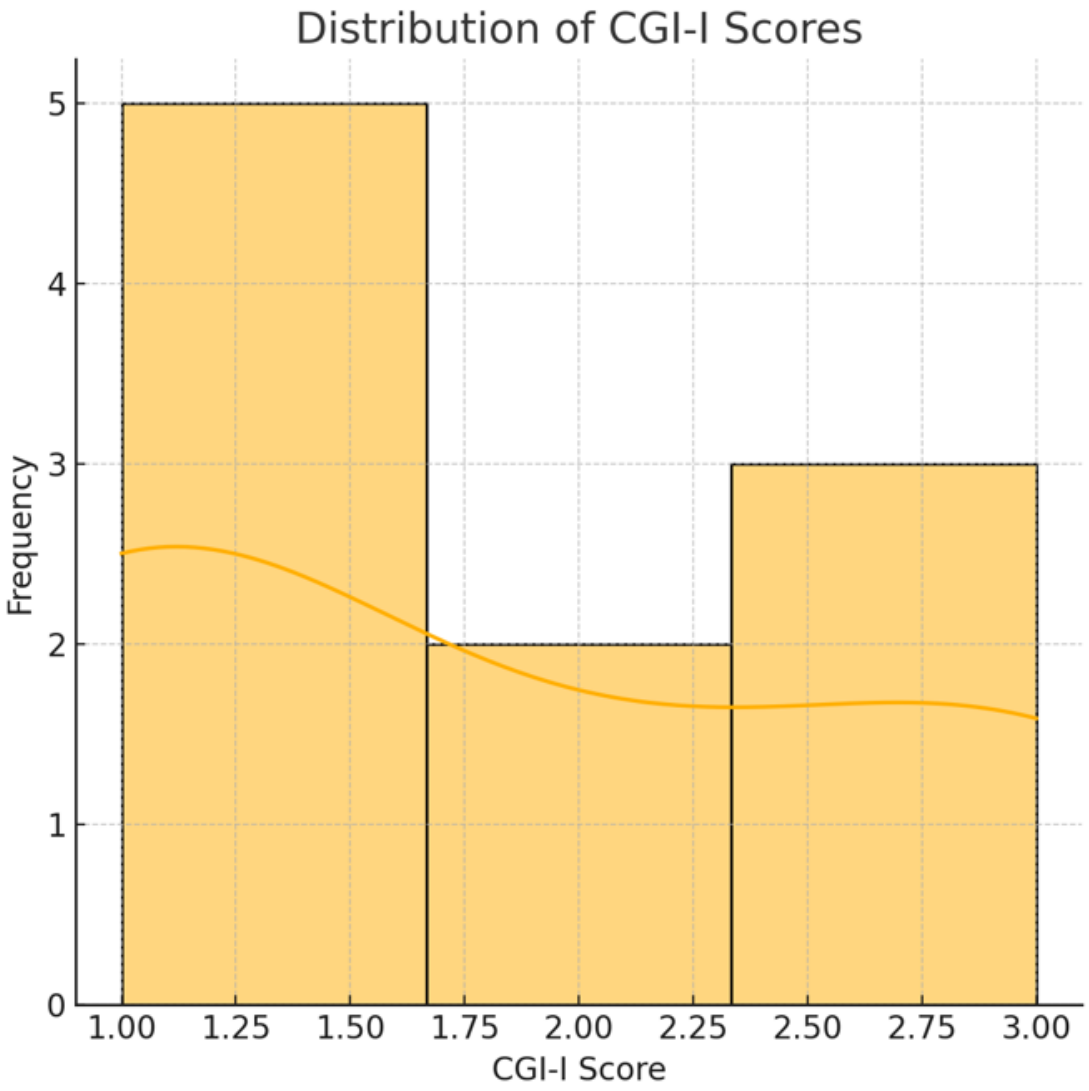


Figure 2.

Distribution of Medication Trials

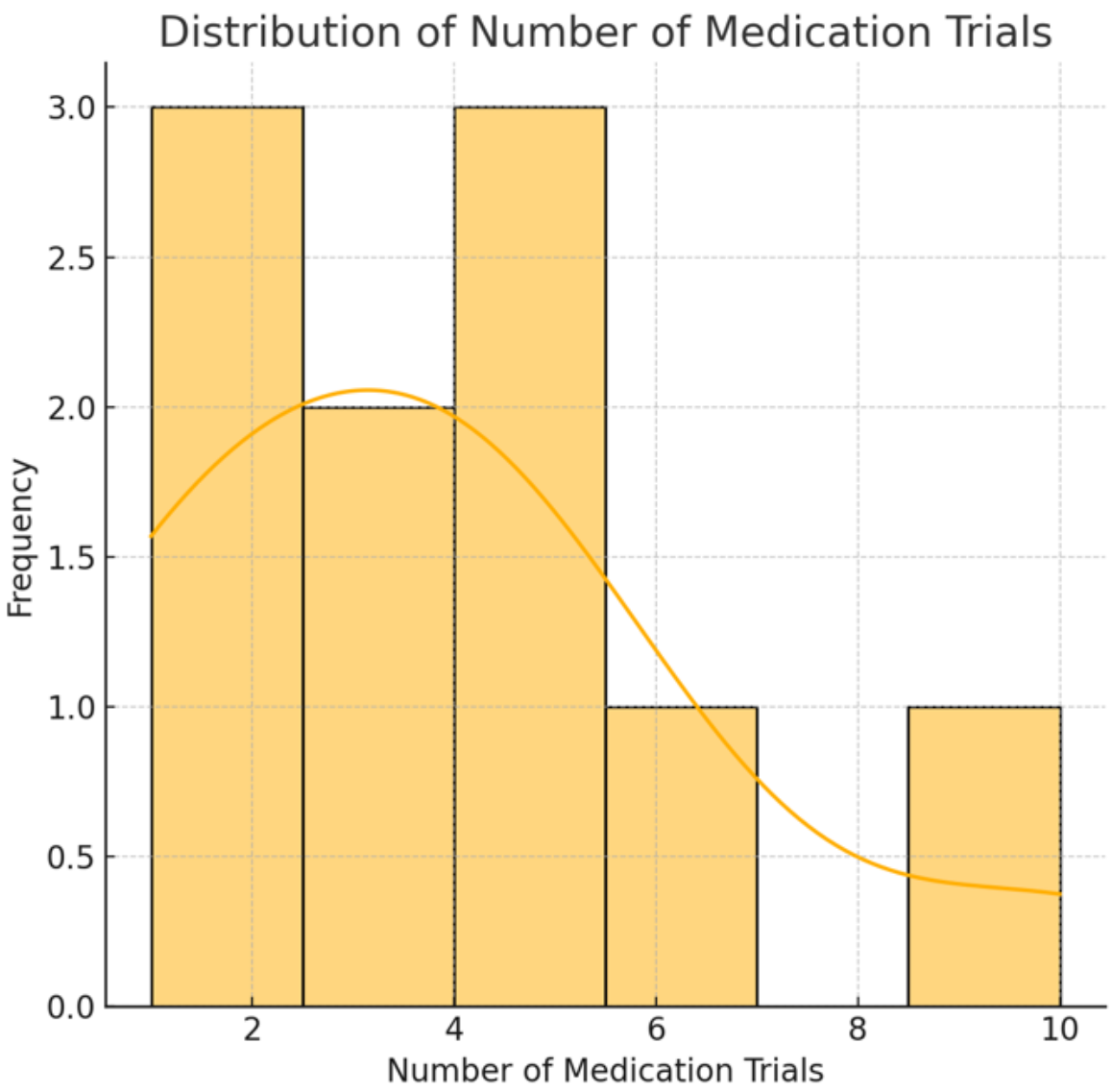


Figure 3.

Correlation Between Medication Trials and CGI-I scores

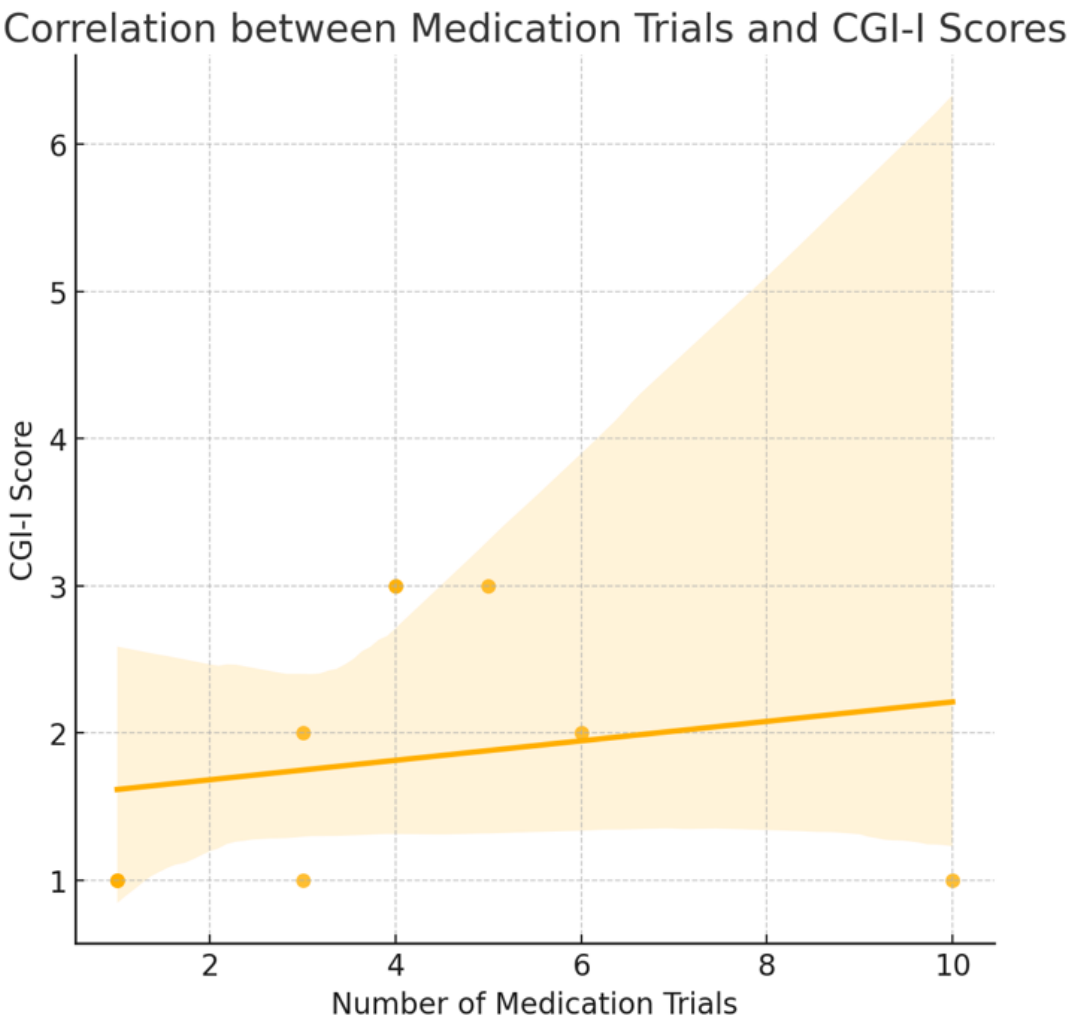


Figure 4.

Correlation Between Medication Trials and Treatment Response

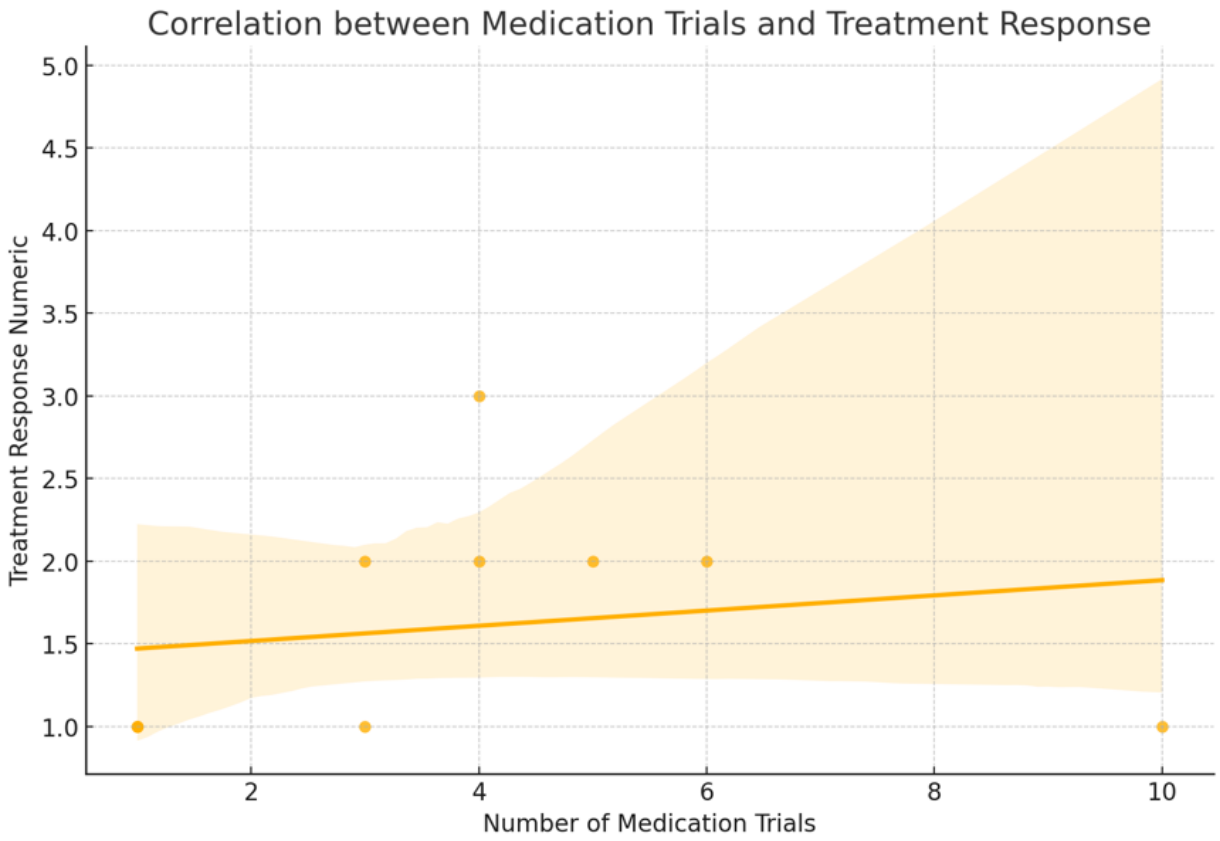


Figure 5.

Average CGI-I Score Comparison

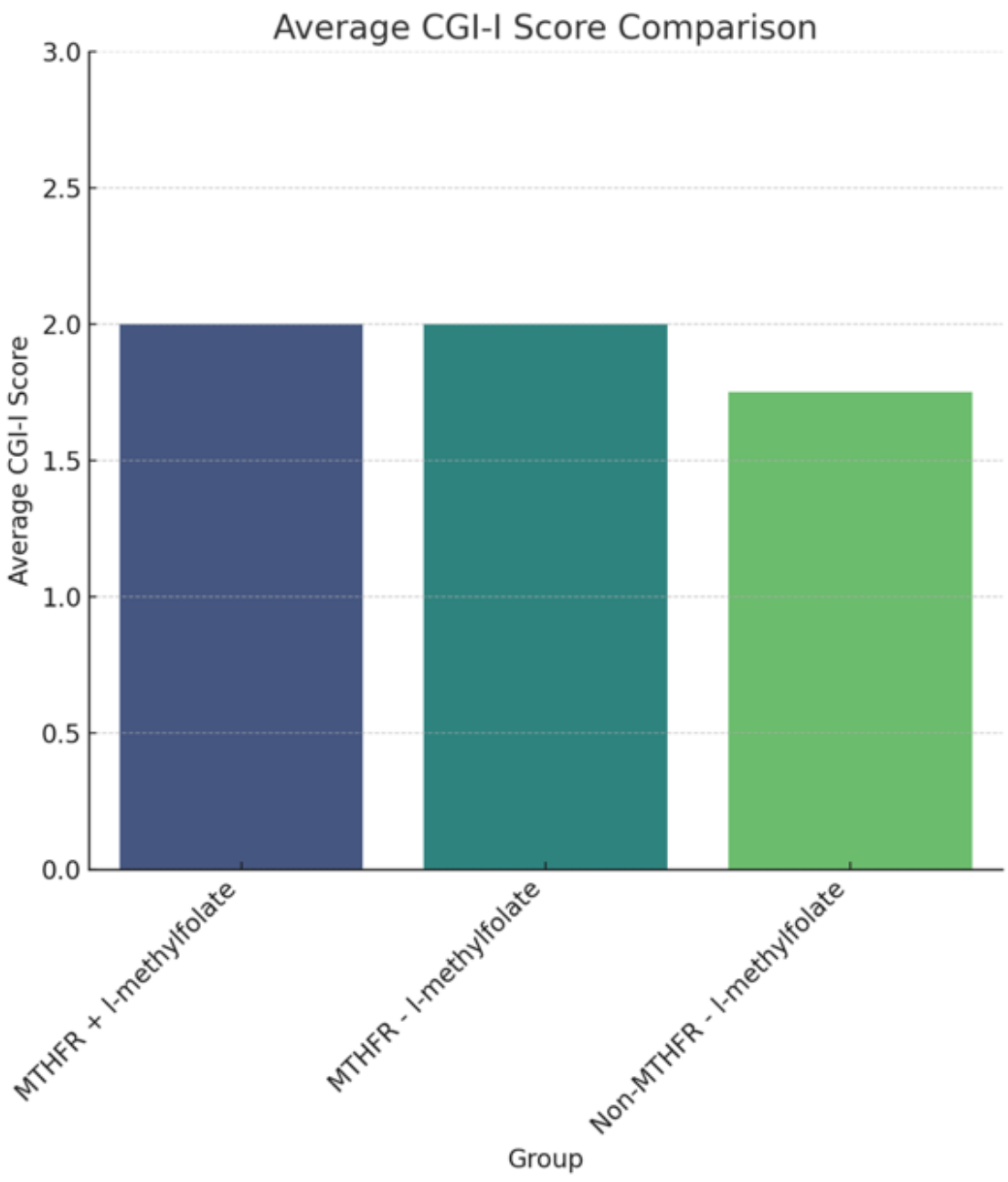
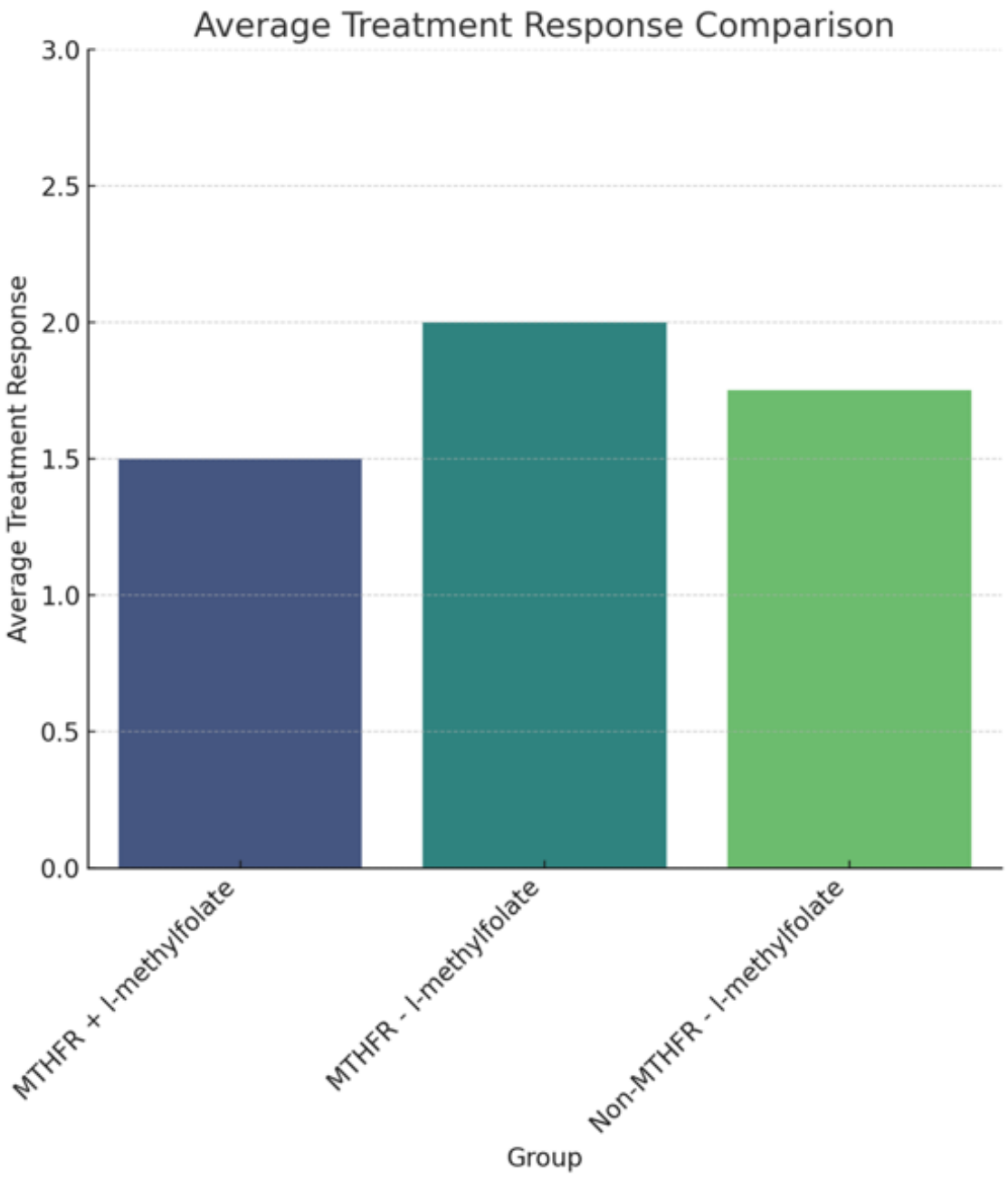


Figure 6.

Average Treatment Response Comparison



Discussion

This QI project, based on clinical outcomes in an outpatient private mental health practice in Miami, FL, aims to increase knowledge of pharmacogenomic testing in child and adolescent psychiatry. The findings highlight several critical insights. The sample demographics indicate a diverse population, predominantly Caucasian/Hispanic, with a slight male majority. The average age of 13.6 years suggests that the sample predominantly consists of adolescents. The high prevalence of ADHD as a primary diagnosis, with comorbid conditions including anxiety, depression, and OCD, emphasizes the complex psychiatric profiles often seen in pediatric mental health settings. This complexity is compounded by significant medical comorbidities in some patients, necessitating a nuanced approach to pharmacological management and overall treatment. As the theoretical framework outlines, incorporating PGx testing into treatment provides greater comfort for patients and their families across multiple physical, emotional, and mental facets.

Utilizing PGx testing through tests like Genomind, Tempus, Toolbox, and Genesight showed a promising impact on treatment outcomes. Specifically, marked improvement in medication response was noted in 50% of the patients, with moderate improvement in an additional 40%. These results suggest that PGx testing can enhance treatment efficacy by tailoring medication choices based on an individual's genetics. The distribution analysis indicates that most patients underwent multiple medication trials before achieving an optimal response. These results align with the typical clinical challenge of finding the proper medication through a trial-and-error process. However, the weak positive correlation between the number of medication trials and CGI-I scores, although not statistically significant, suggests that more trials might be associated with slightly worse treatment responses. This finding emphasizes the

potential benefit of PGx testing in reducing the number of trials needed to find an effective medication.

The correlation analysis revealed weak relationships between specific genetic variants and side effects. For example, the SLC6A4 L(A)/S variant showed a weak negative correlation with gastrointestinal side effects, while the BDNF Val/Met variant showed a weak negative correlation with anxiety symptoms. Although these correlations were not statistically significant, they highlight potential areas for further investigation. Findings regarding the SLC6A4 gene align with prior research demonstrating varying side effect responses related to gene variations (Kronenberg et al., 2007; Owley et al., 2009; Rotberg et al., 2013; Sugie et al., 2005). Understanding these relationships could lead to more precise predictions of side effects based on genetic profiles, improving patient experience and adherence to treatment.

The regression analysis aimed to predict treatment response based on genetic variants and the number of medication trials. While the model's R-squared value suggests that the selected features explain a substantial portion of the variability in treatment response, the lack of statistical significance in the genetic predictors highlights the complexity of psychiatric treatment response. The significant intercept suggests a baseline treatment response, reinforcing the need for a larger sample size to enhance the model's accuracy.

The analysis of the MTHFR variant provided notable insights. Patients with MTHFR variants prescribed supplemental L-methylfolate showed a slightly better average treatment response than those not prescribed the supplement. This finding supports the potential benefit of L-methylfolate supplementation in patients with MTHFR variants. However, the small sample size limits the generalizability of these results. Additional research with a larger cohort is

necessary to validate these findings and refine treatment guidelines. Furthermore, patients prescribed supplemental L-methylfolate had better average treatment response than those not prescribed the supplement without the MTHFR variant. This finding suggests that L-methylfolate may have broader benefits beyond genetic predispositions. It supports consideration for its use in a more comprehensive range of patients, highlighting the importance of a holistic and personalized approach to psychiatric treatment. Further research is essential to validate these findings and guide clinical practice.

Limitations

Limitations of this study include the small sample size and the retrospective nature of the data. These limitations may introduce biases and restrict the generalizability of the findings. Future research should focus on larger, prospective studies to explore these initial findings and examine the impact of PGx testing on long-term outcomes in child and adolescent psychiatry. Additionally, investigating the cost-effectiveness of PGx testing could support its broader adoption in clinical practice.

Implications for Advanced Practice Nursing

Children and adolescents are among the most vulnerable populations, with their rates of mental illness increasing exponentially. Due to the complexity of treating psychiatric disorders, patients often face lengthy medication trials until treatment is optimized. Advanced practice nurses play a crucial role in increasing accessibility and improving the quality of care for pediatric patients facing mental health challenges. The results of this project have meaningful implications for psychiatric advanced practice nursing. Integrating PGx testing in clinical practice can enhance the precision of psychopharmacological treatment, potentially reducing the

number and duration of medication trials. This personalized approach can improve clinical outcomes, treatment adherence, and overall quality of life. Advanced practice nurses can adopt PGx testing, educate patients and families about its benefits, and advocate for broader implementation in clinical settings.

Conclusions

This QI project provides valuable insights into the potential benefits of PGx testing in child and adolescent psychiatry. While further research is needed, the initial findings suggest that PGx testing can enhance treatment precision, reduce trial-and-error medication adjustments, and improve patient outcomes. These findings support the integration of PGx testing into routine clinical practice. In the future, larger scale studies should focus on long-term outcomes of PGx testing in child and adolescent psychiatry.

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Appendix A

Florida International University Institutional Review Board Approval Letter

FIU | FLORIDA INTERNATIONAL UNIVERSITY

Office of Research Integrity
Research Compliance, MARC 430

MEMORANDUM

To:	Dr. Michael Sanchez
CC:	Rebecca Fleisher
From:	Kourtney Wilson, MS, IRB Coordinator KMW
Date:	May 30, 2024
Protocol Title:	"Assessing Utilization and Outcomes of Pharmacogenomic Testing Among Children and Adolescents in Outpatient Psychiatric Treatment: A Quality Improvement Project"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #:	IRB-24-0274	**IRB Exemption Date:**	05/30/24
TOPAZ Reference #:	114150		

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

KMW

Appendix B

CITI Certification

CITI PROGRAM

Completion Date 30-Sep-2021
Expiration Date 29-Sep-2024
Record ID 45401721

This is to certify that:

Rebecca Fleisher

Not valid for renewal of certification through CME.

Has completed the following CITI Program course:

Basic/Refresher Course - Human Subjects Research
(Curriculum Group)
Biomedical Human Research Course
(Course Learner Group)
1 - Basic Course
(Stage)

Under requirements set by:

Florida International University

CITI
Collaborative Institutional Training Initiative

101 NE 3rd Avenue, Suite 320
Fort Lauderdale, FL 33301 US
www.citiprogram.org

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