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Real-world experience of using combinatorial pharmacogenomic test in children and adolescents with depression and anxiety

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ABSTRACT

Objective: To evaluate the real-world impact of using a commercially available combinatorial pharmacogenomic (CPGx) test on medication management and clinical outcomes in children and adolescents treated at a tertiary care psychiatry practice.

Methods: A retrospective cohort study using our prospectively maintained database of patients undergoing CPGx testing was performed. Only patients with clinical data at the time of ordering CPGx test (pre-baseline), potential medication change visit (baseline) and 8-weeks follow-up (post-baseline) visit were included. Clinical Global Impression (CGI) scores for each visit were calculated. Appropriate statistical analysis, including one-sample *t*-test, paired *t*-test and Chi-square test was performed.

Results: Based on the inclusion criteria, 281 (75.9%) of the 370 patients with CPGx testing were included. Their mean age was 15.8 ± 4.5 years (111 females; 39.5%). The average number of medications significantly increased to 2.4 ± 1.2 on the post-baseline visit [$t(280) = 8.34$, $p < 0.001$). Medications were added in 123 (43.7%), replaced in 92 (32.7%) patients and remained unchanged in rest. There was no significant association between medication-related adverse effects and psychotropic medication change group ($p = 0.27$). The study population showed a significant improvement ($p < 0.001$) in the CGI severity, efficacy, and global improvement indices.

Conclusion: In our experience of using CPGx test in a large cohort of children and adolescents during routine clinical practice, three-quarter of them underwent medication change. Additionally, we noted an improvement in clinical outcomes without impacting adverse effects. While the role of clinical judgement in medication changes in our cohort is likely, CPGx may supplement clinical decision making. However, the best use and benefit of CPGx in routine clinical practice needs further investigation.

1. Introduction

Mood and anxiety disorders are highly prevalent among the children and the adolescent population in the last two decades. Mental health treatment remains a 'trial and error' practice. Genetic variation is one of the several variables that may impact a medication's efficacy by affecting its metabolism (pharmacokinetics) or mechanism of action (pharmacodynamics). Pharmacogenomics is a rapidly developing branch of personalized medicine that has emerged from the need to minimize this 'trial and error' approach. It aims to identify safe and effective drug treatment regimens based on everyone's unique genetic makeup. Apart from individual gene tests for specific gene-drug interactions, we now have commercial availability of combinatorial pharmacogenomic tests (CPGx) designed to analyze multiple genes involved in the metabolism of multiple drugs (Benitez et al., 2018; Hall-Flavin et al., 2012; Jablonski et al., 2018). A recent blinded, randomized controlled trial (RCT) of 1167 patients found the significantly higher response and remission rates of mood disorder among patients undergoing medication change guided by GeneSight® (AssurexHealth, OH, USA) CPGx test compared to treatment as usual (TAU) (Greden et al., 2019). Several studies show economic benefit and healthcare cost reduction using a CPGx guided therapy (Benitez et al., 2018; Brown et al., 2017; Winner et al., 2015). However, a recent meta-analysis of published RCT and open-label studies found that they are all

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industry-funded studies with differences in results of blinded versus unblinded studies (Rosenblatet al., 2018). Additionally, CPGx guided therapy use has not been directly investigated in children and adolescent population (Namerow et al., 2020). the American Academy of Child and Adolescent Psychiatry (AACAP) recently released a policy statement recommending "Clinicians avoid using pharmacogenetic testing to select psychotropic medications in children and adolescents" (AACAP webpage).

However, several experts, including Clinical Pharmacogenetics Implementation Consortium (CPIC), countered this position and recommended taking a more nuanced approach to integrate the CPGx test findings into children and adolescents psychiatric care, while keeping clinical evaluation and judgment as to the cornerstone of management. (Ramsey et al., 2020; Hicks et al., 2015). Despite the lack of consensus on the use and utility of CPGx testing and the absence of clinical trials, unlike adults, in child and adolescent psychiatric care, many institutions use the guidelines by FDA and CPIC for dosing psychotropics drugs based on pharmacokinetic genes in their practice (Ramsey et al., 2020). Therefore, there is a critical need for understanding the use and benefit of pharmacogenomic testing in child and adolescent psychiatry clinics. Our paper aims to fill this knowledge gap by reporting our real-world experience of the use of CPGx in routine clinical care in a child and adolescent psychiatry clinic.

2. Materials and methods

2.1. Study population and data collection

After the Institutional Review Board (IRB) approval, we used our prospectively maintained database of patients undergoing GeneSight® testing in the child and adolescent psychiatry clinics at the Cleveland Clinic from January 09, 2015 to 08/31/2019. GeneSight® Psychotropic test is a commercially available CPGx test which analyzes the genotypes of 59 alleles and variants across 6 pharmacokinetic genes and 2 pharmacodynamic genes (Jablonski et al., 2018). Patients with clinical diagnoses of major depressive disorder (excluding bipolar depression) or generalized anxiety disorder as per the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) were included in the analysis.

Electronic medical records (EMR) of all these patients were reviewed to extract demographical and clinical variables.

Clinic visit on which psychotropic medications were changed based on CPGx results was considered the baseline visit. The immediately preceding clinic visit when CPGx was ordered was considered pre-baseline and the follow up visit 8-weeks later was the post-baseline visit. Data on psychotropic medications used at the time of pre-baseline, baseline, and post-baseline clinic visit was extracted. For the purposes of clinical interpretation, CPGx test provides the medications tested for in three advisory groups ("bins") of 'use as directed' (Green bin), 'moderate gene-drug' interaction' (Yellow bin), and 'significant gene-drug interaction' (Red bin). For the patients undergoing medication replacement, we identified the bin to which medication replaced and the new medication belonged to in the CPGx report.

Clinical Global Impression (CGI) scores, including the severity scale, improvement scale and efficacy index (Guy, 1976) were retrospectively calculated from the clinic encounter documentation at the time of above-mentioned clinic visits by two authors (AD and SC), independently. Based on CPGx testing, the medication management on the baseline visit was categorized as added, replaced, or unchanged.

2.2. Data analysis

Categorical variables were described using frequencies and percentages, whereas continuous variables, depending on distribution, were described using mean and standard deviation (SD) or medians and quartiles (first-third quartiles). The CGI scores for the three indices were averaged for the study population at each visit type. The differences between the various CGI scores at post-baseline and baseline clinic visits were computed by subtracting the latter from the former. Since a lower CGI score signifies better status, a negative value of mean difference suggests an improvement. Although CGI is an ordinal scale, the methods of repeated measures mixed models were used to test the differences in mean Genesight scores for severity and improvement. Tukey-Kramer adjustments were made to correct for multiple comparisons of mean responses. The change in psychotropic medication burden from pre-baseline to baseline visit was calculated using paired *t*-test. Chi-square test of independence was used to compare the difference in medication-related adverse effects between the patients who underwent addition, replacement, or no change for psychotropic medication.

3. Results

GeneSight test was performed on a total of 370 patients during the study period. Based on the inclusion criteria, 281 (75.9%) of the 370 patients were included in the study with a mean age of 15.8 ± 4.5 years (111 females; 39.5%). The demographical data of the study population are provided in Table 1.

The average number of medications on the pre-baseline (before CPGx) visit was 2.1 ± 1.1, which significantly increased to 2.4 ± 1.2 on the post-baseline (after CPGx) visit [$t(280) = 8.34$, $p < 0.001$). Based on the CPGx testing, medications were added in 123 (43.7%) patients, replaced in 92 (32.7%) patients, and remained unchanged in 66 (23.5%) patients. In all instances of medication addition, it belonged to the 'Green' bin. Among 92 patients undergoing medication replacement, the switch was made from 'Red' to 'Green' bin in 14 (15.2%) patients, 'Yellow' to 'Green' bin in 44 (47.8%), 'Red' to 'Yellow' bin in 24 (26.1%) patients, 'Yellow' to 'Yellow' bin in 3 (3.3%) and 'Green' to 'Green' bin in 7 (7.6%) of patients.

Medication-related adverse effects were reported by 38 (13.5%) patients in total at the time of post-baseline visit, including 21 (17.1%) in the addition group, 11 (12%) in the replacement group, and 6 (9.1%) patients in the unchanged group. A chi-square test of independence showed that there was no significant association between medication-related adverse effects and psychotropic medication change group [$\chi^2(2, N = 281) = 2.62$, $p = 0.27$].

Table 2 presents the CGI scores at the various clinic visits. The mean change in CGI severity, efficacy, and global improvement at the post-baseline visit, compared to baseline, was −0.26 (SD ± 0.95), −2.42 (SD ± 5.02), and −0.99 (SD ± 2.32), respectively. The study population showed a significant improvement ($p < 0.001$) in the CGI severity, efficacy, and global improvement indices.

4. Discussion

We present one of the largest, real-world experience of the use of CPGx test in close to 300 patients seen in child and adolescent psychiatry clinics at a tertiary care center. The study population showed an overall

Table 1
Demographics of the study population.

Characteristic	No. of patients (N = 281) (%)
Age (yr)± SD	15.8 ± 4.5
Male	170 (60.5)
Race	
White	221 (78.6)
African-American	22 (7.8)
Asian	2 (0.7)
Multiracial	21 (7.5)
Unknown	15 (5.3)
Ethnicity	
Non-Hispanic	256 (91.1)
Hispanic	21 (7.5)
Unknown	4 (1.4)

Table 2
Mean CGI index scores at various clinic visits.

CGI category	Pre-baseline clinic visit	Baseline Clinic visit	Post-baseline clinic visit
Severity	4.23	4.18	3.92
Efficacy	8.16	8.75	6.34
Global improvement	3.95	4.27	3.26

improvement in clinical outcomes after changes in medication based on the results of CPGx testing without a significant increase in adverse effects. This is comparable to a recent meta-analysis of 1556 adults (≥18 years), which concluded that CPGx guided care improves outcomes among patients with major depressive disorder (Brown et al., 2020). The use of CPGx led to a significant increase in medication burden in the overall study population, which includes close to one-third (32.7%) of patients where a psychotropic medication was replaced. Additionally, no medication changes were made in almost a quarter (23.5%) of the patients. Combined, the psychotropic medication management after CPGx testing suggests that psychiatrists in the real-world settings are using their clinical judgment and are not solely relying on CPGx testing. This is in line with the recent recommendations proposed by an expert panel (Ramsey et al., 2020). Additionally, the analysis of medication replacements suggests that the CPGx test is not used as a 'one size fits all' whereby every patient is changed from a 'Red' to 'Green' bin (see Methods section). Rather, the clinicians seem to be taking a pragmatic approach whereby nuanced clinical decisions are made within the context of CPGx test results.

A recent study analyzing data of close to seven hundred thousand children and adolescents found a steady increase in psychotropic polypharmacy affecting 24.4% of the participants (Soria Saucedo et al., 2018). Balancing the benefits and risks of polypharmacy is a challenging clinical task as it is associated with significant adverse effects (Olashore et al., 2017). We found that although CPGx seems to overall contribute to polypharmacy in routine clinical practice, there was no significant difference in the adverse events among patient groups undergoing addition, replacement or no change in psychotropic medications. Overall, adverse events were reported by close to 14% of patients, which is consistent with literature (Hilt et al., 2014). However, it is important to remember that tests like CPGx provide information on genetic influence on drug metabolism, which may not precisely correlate with individual's tolerability to side effects. Therefore, close adverse effect monitoring remains critical after medication change based on CPGx test. It is especially important if there is potential risk of polypharmacy as noted by us in this study.

The study found that clinical outcomes improved significantly on all CGI indices on the post-baseline visit. We used CGI scoring to determine the patient's global functioning before and after CPGx-guided treatment due to the retrospective methodology of our study. CGI is a validated tool in the clinical settings (Jones et al., 2020), correlates well with self-rated valid scales (Leon et al., 1993; Khan et al., 2002) and shown as a robust tool for retrospective assessment of clinical outcomes (Kelly, 2010). Various studies with different population sources and different ascertainment methods of the overall improvement provide extensive variation in CPGx guided care use compared to treatment as usual. Several studies have explored overall clinical improvement in people with psychotropic guided care using blood test (Rothschild et al., 2021; Shelton et al., 2020); some used self-validated scales (Hall-Flavin et al., 2012; Winner et al., 2013), and another used CGI (Blasco-Fontecilla, 2019). The latter is a small sample study, which similarly to us, analyzed 20 children and adolescents seen in routine clinical practice (Blasco--Fontecilla, 2019). Similar to our experience, the authors in a large study sample found improvement in clinical outcomes but additionally, and unlike us, noted a reduction in psychotropic medication burden. The difference in medication burden between the two studies could be a function of small sample size or different disease severity. Being a tertiary care referral center, our patient population is likely to skew towards a higher disease severity.

Medication impact on clinical outcomes depends on multiple factors, including age, dosing, drug-drug interactions, etc. Gene-medication interaction can impact pharmacokinetics as well as pharmacodynamics of the drug. While the field of pharmacogenomics is in flux, the Food and Drug Administration (FDA) already recommends pharmacogenomic-based assessment of severe hypersensitivity reaction risk and dose adjustments for several psychotropic medications (Hilt et al., 2014). Despite the known benefits of the use of individual gene analysis in clinical psychiatry, the use of tests that analyze the combined impact of variation in multiple genes, i.e., CPGx remains controversial. This is best highlighted by the recent AACAP position against the use of CPGx in routine clinical care. However, the evidence seems to be accumulating the CPGx is a superior predictor of clinical outcomes compared to individual gene analysis (Rothschild et al., 2021). Currently CPGx is covered by Medicaid, Medicare Part B and a growing list of commercial insurances. However, before tests like CPGx become standard of care, it is important to perform robust cost vs. benefit analysis at a population level to determine their usefulness to society-at-large.

There are several limitations to our study, including its retrospective and naturalistic design. Due to the retrospective nature of the study, we were not able to prospectively analyze changes in patient outcomes and had to rely on the information documented in the EMR. Additionally, while the naturalistic design helps to capture a real-world use data, it may preclude from making accurate and precise conclusion of the true value of an intervention like CPGx test in the management of patients with psychiatric comorbidities. We did not stratify the study population into depression and anxiety. This was avoided because our goal was to analyze the real-world use of CPGx testing to aid clinical decision-making. Patients whose medication doses were adjusted without addition or replacement of a medication were classified as "unchanged" group to avoid making multiple group comparisons. A vast majority of the patients were Caucasians, which may limit the generalizability of the study finding. Despite the limitations, in our experience of using CPGx test in children and adolescents with anxiety and depression, a large majority underwent medication management change. Additionally, improved clinical outcomes without impact on adverse effects was noted. While we were not able to assess the role of clinical judgement in medication changes made in our cohort, CPGx seems to supplement clinical decision making. However, the best use and benefit of CPGx in routine clinical practice needs further investigation.

Disclosure of conflicts of interest

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"We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines."

Author statement

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Amit Anand: Conceptualization; Investigation; Methodology; Writing - review & editing.

Tatiana Falcone: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

References

Benitez, J., Cool, C.L., Scotti, D.J., 2018 Nov. Use of combinatorial pharmacogenomic guidance in treating psychiatric disorders. Per Med 15 (6), 481–494.

Blasco-Fontecilla, H., 2019. Clinical utility of pharmacogenetic testing in children and adolescents with severe mental disorders. J. Neural. Transm. 126 (1), 101–107.

Brown, L.C., Lorenz, R.A., Li, J., Dechairo, B.M., 2017 Mar. Economic utility: combinatorial pharmacogenomics and medication cost savings for mental health care in a primary care setting. Clin. Therapeut. 39 (3), 592–602.

Brown, L., Vranjkovic, O., Li, J., Yu, K., Al Habbab, T., Johnson, H., Brown, K., Jablonski, M.R., Dechairo, B., 2020 Jun. The clinical utility of combinatorial pharmacogenomic testing for patients with depression: a meta-analysis. Pharmacogenomics 21 (8), 559–569.

Greden, J.F., Parikh, S.V., Rothschild, A.J., Thase, M.E., Dunlop, B.W., et al., 2019 Jan 4. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J. Psychiatr. Res. 111, 59–67.

Guy, William, 1976. Clinical Global Impressions". ECDEU Assessment Manual for Psychopharmacology—Revised. U.S. Department of Health, Education, and Welfare; Public Health Service, Rockville, MD. Alcohol; Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs. pp. 218–222. OCLC 2344751. DHEW Publ No ADM 76–338 – via Internet Archive. https://www.aacap.org/AACAP/Policy_Statements/2020/Clinical-Use-Pharmacogenetic-Tests-Prescribing-Psychotropic-Medications-for-Children-Adolescents.aspx. Accessed 4/21/21.

Hall-Flavin, D.K., Winner, J.G., Allen, J.D., et al., 2012 Oct 16. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl. Psychiatry 2 (10), e172.

Hicks, J.K., Bishop, J.R., Sangkuhl, K., et al., 2015. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin. Pharmacol. Ther. 98, 127–134.

Hilt, R.J., Chaudhari, M., Bell, J.F., Wolf, C., Koprowicz, K., King, B.H., 2014 Mar. Side effects from use of one or more psychiatric medications in a population-based sample of children and adolescents. J. Child Adolesc. Psychopharmacol. 24 (2), 83–89.

Jablonski, M.R., King, N., Wang, Y., Winner, J.G., Watterson, L.R., Gunselman, S., Dechairo, B.M., 2018 May 1. Analytical validation of a psychiatric pharmacogenomic test. Per Med 15 (3), 189–197.

Jones, R.M., Gerritsen, C., Maheandiran, M., Simpson, A.I.F., 2020 Mar 20. Validation of the clinical global impression-corrections scale (CGI-C) by equipercentile linking to the BPRS-E. Front. Psychiatr. 11, 180.

Kelly, P.J., 2010. Calculating clinically significant change: applications of the Clinical Global Impressions (CGI) Scale to evaluate client outcomes in private practice. Clin. Psychol. 14 (3), 107–111.

Khan, A., Khan, S.R., Shankles, E.B., Polissar, N.L., 2002. Relative sensitivity of the montgomery-asberg depression rating scale, the Hamilton depression rating scale and the clinical global impressions rating scale in antidepressant clinical trials. Int. Clin. Psychopharmacol. 17 (6), 281–285.

Leon, A.C., Shear, M.K., Klerman, G.L., et al., 1993. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. Journal of Clinical Psychopharmacology 13 (5), 327–331.

Olashore, A.A., Rukewe, A., 2017 May 10. Polypharmacy among children and adolescents with psychiatric disorders in a mental referral hospital in Botswana. BMC Psychiatr. 17 (1), 174.

Ramsey, L.B., Namerow, L.B., Bishop, J.R., Hicks, J.K., Bousman, C., Croarkin, P.E., Mathews, C.A., Van Driest, S.L., Strawn, J.R., 2020 Aug 26. Thoughtful clinical use of pharmacogenetics in child and adolescent psychopharmacology. J. Am. Acad. Child Adolesc. Psychiatry (20), S0890–S8567.)31357-5.

Rothschild, A.J., Parikh, S.V., Hain, D., Law, R., Thase, M.E., Dunlop, B.W., DeBattista, C., Conway, C.R., Forester, B.P., Shelton, R.C., Macaluso, M., Brown, K., Lewis, D., Gutin, A., Jablonski, M.R., Greden, J.F., 2021 Feb. Clinical validation of combinatorial pharmacogenomic testing and single-gene guidelines in predicting psychotropic medication blood levels and clinical outcomes in patients with depression. Psychiatr. Res. 296, 113649.

Shelton, R.C., Parikh, S.V., Law, R.A., Rothschild, A.J., Thase, M.E., Dunlop, B.W., DeBattista, C., Conway, C.R., Forester, B.P., Macaluso, M., Hain, D.T., Aguilar, A.L., Brown, K., Lewis, D.J., Jablonski, M.R., Greden, J.F., 2020 Aug. Combinatorial pharmacogenomic algorithm is predictive of citalopram and escitalopram metabolism in patients with major depressive disorder. Psychiatr. Res. 290, 113017.

Soria Saucedo, R., Liu, X., Hincapie-Castillo, J.M., Zambrano, D., Bussing, R., Winterstein, A.G., 2018 Aug 1. Prevalence, time trends, and utilization patterns of psychotropic polypharmacy among pediatric Medicaid beneficiaries, 1999-2010. Psychiatr. Serv. 69 (8), 919–926.

Winner, J., Allen, J.D., Altar, C.A., Spahic-Mihajlovic, A., 2013. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl. Psychiatry 3 (3), e242.

Winner, J.G., Carhart, J.M., Altar, C.A., Goldfarb, S., Allen, J.D., Lavezzari, G., Parsons, K.K., Marshak, A.G., Garavaglia, S., Dechairo, B.M., 2015. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Curr. Med. Res. Opin. 31 (9), 1633–1643.