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Pharmacogenomic Profiling of Pediatric Patients on Psychotropic Medications in an Emergency Department

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Objective: The aim of the study was to evaluate the ability of a combinatorial pharmacogenomic test to predict medication blood levels and relative clinical improvements in a selected pediatric population.

Methods: This study enrolled patients between ages 3 to 18 years who presented to a pediatric emergency department with acute psychiatric, behavioral, or mental health crisis and/or concerns, and had previously been prescribed psychotropic medications. Patients received combinatorial pharmacogenomic testing with medications categorized according to gene-drug interactions (GDIs); medications with a GDI were considered "incongruent," and medications without a GDI were considered "congruent." Blood levels for escitalopram, fluoxetine, aripiprazole, and clonidine were evaluated according to level of GDI. Relative clinical improvements in response to the prescribed psychotropic medications were measured using a parent-rated Clinical Global Impression of Improvement (CGI-I) assessment, where lower scores corresponded with greater improvement.

Results: Of the 100 patients enrolled, 73% reported taking ≥1 incongruent medication. There was no significant difference in CGI-I scores between patients prescribed congruent versus incongruent medications (3.37 vs 3.68, $P = 0.343$). Among patients who presented for depression or suicidal ideation, those prescribed congruent medications had significantly lower CGI-I scores compared with those taking incongruent medications ($P = 0.036$ for depression, $P = 0.018$ for suicidal ideation). There was a significant association between medication GDI and blood levels for aripiprazole (n = 15, $P = 0.01$) and escitalopram (n = 10, $P = 0.01$).

Conclusions: Our preliminary findings suggest that combinatorial pharmacogenomic testing can predict medication blood levels and relative outcomes based on medication congruency in children presenting to an emergency department with acute psychiatric/behavioral crises. Additional studies will be needed to confirm these findings.

Key Words: combinatorial pharmacogenomic testing, psychiatric disorders, psychotropic medications, pediatric population, blood levels

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Pharmacogenomic testing is becoming more common in psychiatric settings to guide medication selection in adults. The impact of genetic variation on drug safety and efficacy has been well established for a variety of psychotropic medications, and several organizations, including the Clinical Pharmacogenetic Implementation Consortium (CPIC), provide dosing recommendations based on phenotypes for individual genes.[1–3] In pediatric patients, recommendations surrounding the use of pharmacogenomic testing to guide psychotropic medication selection are mixed,[4–6] and professional organizations have questioned whether pharmacogenomic testing is appropriate in the pediatric population.[7] Despite concerns, the potential for individualized treatment to improve clinical outcomes in the pediatric population warrants further exploration.

Medication selection and dosing for psychiatric and behavioral conditions are challenging because adverse reactions can often result in patient noncompliance and treatment failure.[4,8,9] As such, medications in pediatric patients are typically initiated at a low dose, with a slow upward taper. This approach can lead to underdosing[10] and, consequently, a longer duration to achieve efficacy, potentially resulting in increased emergency department visits and/or hospitalizations for psychiatric reasons (eg, suicide attempts, aggressive behavior).[11] Even with medication management, remission rates in pediatric mental health conditions (ie, depression, anxiety, bipolar disorder, and attention-deficit/hyperactivity disorder [ADHD]) range from 16% to 66%.[12–14] Although a variety of

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Data availability: The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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factors may influence medication treatment success, this range conservatively suggests that at minimum, one third of patients do not achieve remission. Implementing pharmacogenomic testing in this population may improve clinical outcomes by identifying gene-drug interactions (GDIs), which can be used to guide medication selection and dosing to increase the likelihood that patients will benefit from medication management.

Studies in pediatric patients have found that variants in genes related to medication metabolism (ie, pharmacokinetics) and mechanism of action (ie, pharmacodynamics) are associated with medication response, adverse effects, and tolerability.[11,15] Although phenotypes and recommendations based on individual genes can be useful, a more comprehensive assessment of GDIs based on multiple genes can be achieved through combinatorial pharmacogenomic (CPGx) testing. The CPGx test provides recommendations using a weighted algorithm based on multiple genes involved in the pharmacokinetic and pharmacodynamic aspects of a particular medication. In adults with depression, clinical validation studies have demonstrated that the CPGx test predicts medication blood levels,[16–18] and clinical utility studies have shown improved outcomes when treatment is guided by CPGx testing compared with treatment as usual.[19–21] In pediatric patients with depression, findings have been mixed, with no clear evidence to support the utility of CPGx testing in this population.[22,23] To appropriately assess the clinical utility and validity of CPGx testing in pediatric patients with depression, anxiety, and other psychiatric disorders, additional studies will be needed. No previous studies have reported on the utility of CPGx testing in pediatric patients presenting in crisis to a pediatric emergency department (PED), potentially highlighting a vulnerable cohort where GDIs may be impacting medication response. Indeed, PED visits for mental health and behavioral complaints, including suicidality and self-harm, have increased over the last decade.[24,25] With the exacerbation of this trend by the onset of the COVID-19 pandemic,[26] there may be an opportunity for PED health care to include personalized medication treatment to improve mental health outcomes in this population.

Here, we present a cross-sectional pilot study on the ability of a CPGx test to predict medication blood levels and relative improvements in pediatric patients presenting to a PED with acute psychiatric and behavioral emergencies; all included patients presented for treatment of a psychiatric disorder that was being managed with medication.

METHODS

Cohort

All patients enrolled in this study presented to the Children's of Alabama PED at the University of Alabama at Birmingham (UAB) over an 18-month period. Patients were eligible for enrollment if they were 3 to 18 years of age, had been prescribed ≥1 psychotropic medications (ie, antidepressants, antipsychotics, and medications for ADHD), and presented with a mental health, behavioral, or psychiatric concern. Patients were excluded if they presented with acute drug or alcohol intoxication, were in Alabama Department of Human Resources custody, or were medically unstable. Blood and buccal samples were collected for CPGx and blood levels testing during the PED visit.

This study was approved by the UAB Institutional Review Board. Informed consent was obtained from all patients before participating in the study. Signed and dated written informed consent was obtained from each patient, parent, or legal guardian before enrollment. Assent was obtained for patients between 7 and 13 years of age.

Pharmacogenomic Testing

All patients were tested with the GeneSight Psychotropic and GeneSight ADHD panels (Myriad Neuroscience, Mason, Ohio).[27] Tests were performed in a Clinical Laboratory Improvement Amendments– and College of American Pathologists–accredited laboratory. The test was developed, and its performance characteristics were determined by Assurex Health. The GeneSight Psychotropic test included evaluation of genotypes for 58 alleles and variants across 8 genes, and the GeneSight ADHD test included evaluation of genotypes for 20 alleles and variants across 3 genes (see Supplemental Materials, http://links.lww.com/PEC/B46).

For each medication, a combined phenotype was assigned based on a weighted algorithmic assessment of multiple pharmacokinetic and pharmacodynamic genes. On the test report, medications were categorized according to combined level of GDI with accompanying footnotes on recommendations for medication use (eg, dosage adjustment). For this study, medications were divided into the following 2 categories based on the combined phenotype: (1) medications with a moderate or significant GDI and (2) medications with no GDI. Medications with a GDI were considered "incongruent," and medications without a GDI were considered "congruent."

Blood Levels

Blood samples were collected for each medication but analysis was only conducted if there were at least 10 patients with recorded blood levels per medication. Blood draws were performed during the PED visit after consent/assent was obtained. Venous blood samples (15–20 mL, 10 mL if the patient was <14 kg) were collected from each patient; 5 mL of the blood collected was reserved for future DNA genomic analyses at the UAB. The samples were then labeled, centrifuged at UAB, stored at −80°C, and were then retrieved by Quest Diagnostics within 48 hours of collection for further analysis. Serum quantitation of psychiatric medication concentrations was performed using liquid chromatography with tandem mass spectrometry at NMS Labs (Willowgrove, Pa) with a reporting threshold of 10 ng/mL.

For the analyses involving blood levels, rather than being categorized based on a combined phenotype using pharmacokinetic and pharmacodynamic genes, medications were categorized based on the level of GDI for pharmacokinetic genes only and the direction of the predicted change in metabolism: (1) GDI with decreased metabolism, (2) GDI with increased metabolism, and (3) no GDI/unknown impact on metabolism.

Data Collection and Analysis

Demographic data included patient age at the time of admission to the PED, sex, race/ethnicity, and weight. Medical history included the following: medication history, indication for psychotropic medication use, and reason for PED visit (eg, anxiety, panic attack, intentional self-injury, suicidal/homicidal ideation, aggression, severe depression). Study data were collected and managed using REDCap electronic data capture tools hosted at the UAB.[28,29] Demographic characteristics were assessed using descriptive statistics and compared between patients prescribed congruent medications (ie, with no GDI) and patients prescribed at least one incongruent medication (ie, with moderate/significant GDI) using χ^2 tests, Fisher exact tests, and *t* tests.

Patient outcomes were evaluated at a single-time point using the Clinical Global Impression–Improvement (CGI-I) survey tool, which was completed by the parent/guardian of the patient during the PED visit. Clinical personnel were present to explain CGI-I questions and scoring to parents/guardians and were available to answer any additional questions and/or assist with completing the questionnaire. The CGI-I was used to determine the degree

of relative improvement of the underlying psychiatric disorder from when the patient began taking the prescribed psychotropic medication(s). The CGI-I is a validated scale that can be used to assess relative improvement for a variety of psychiatric conditions using a single-time point; this scale is designed to provide a measure of relative improvement and therefore does not require a baseline measure. The assessment consisted of a 0- to 7-point scale with the following values: 7 = "very much worse," 6 = "much worse," 5 = "minimally worse," 4 = "no change," 3 = "minimally improved," 2 = "much improved," 1 = "very much improved," and 0 = "not assessed."[30] In this study, no patients were classified as "not assessed." Mean CGI-I scores were calculated and compared among patients taking congruent and incongruent medications according to reason for PED admission using a 2-sample *t* test.

Blood levels for medications with at least 10 blood-drug level samples were analyzed, including the antipsychotic aripiprazole, the selective serotonin reuptake inhibitors escitalopram and fluoxetine, and the ADHD medication, clonidine. To account for variability in medication dosing across patients, concentration/dose ratios were log transformed using the following equation:

$$\mathrm{Log}_{10}\left(\frac{\text{Concentration}}{\text{Dose}}\right)$$

Effect coding was used to weight patients based on their clinical consideration so that the linear trend between predicted and observed relative blood-drug levels could be assessed. Patients with a significant GDI with decreased metabolism were assigned an effect code of 1, patients with a significant GDI with increased metabolism were assigned an effect code of −1, and patients with no/moderate GDI were assigned an effect code of 0. Analysis of variance was used to evaluate the relationship between the effect coded clinical consideration category and log-transformed blood-drug levels for each medication. Analysis of variance was also used to evaluate the relationship between bodyweight, age, sex, or race and log-transformed blood-drug levels for each medication.

Statistical analyses were performed using SAS software (Version 9.4), JMP 15 (SAS Institute), R 3.5.1, and R's "car" package. Two-sided *P* values ≤0.05 were considered statistically significant.

TABLE 1. Demographic Characteristics of Patients Taking Congruent and Incongruent Medications

Patient Demographic	Congruent (No GDI, n = 27)	Incongruent (GDI, n = 73)	Total (N = 100)
Age			
Median	13.00	14.00	14.00
Min–max	5.0–18.0	4.0–18.0	4.0–18.0
IQR	4.0	5.0	5.0
Sex, n (%)			
Female	8 (29.6)	36 (49.3)	44 (44.0)
Male	19 (70.4)	37 (50.7)	56 (56.0)
Race, n (%)			
American Indian/ Alaska Native	1 (3.7)	0	1 (1.0)
Black or African American	8 (29.6)	17 (23.3)	25 (25.0)
White/Caucasian	17 (63.0)	54 (74.0)	71 (71.0)
More than one race	1 (3.7)	2 (2.7)	3 (3.0)
Ethnicity, n (%)			
Hispanic or Latino	1 (3.7)	0	1 (1.0)
Not Hispanic or Latino	24 (88.9)	69 (94.5)	93 (93.0)
Unknown/not reported	2 (7.4)	4 (5.5)	6 (6.0)
Weight			
Median	56.00	62.00	61.00
Min–max	20.0–137.0	18.0–170.0	18.0–170.0
IQR	32.0	32.5	32.25
Reason for PED visit			
Behavioral problem	13 (48.1)	33 (45.2)	46 (46.0)
Depression	15 (55.6)	28 (38.4)	43 (43.0)
Psychiatric evaluation	10 (37.0)	36 (49.3)	46 (46.0)
Suicidal ideation	17 (63.0)	40 (54.8)	57 (57.0)
Violent behavior	9 (33.3)	27 (37.0)	36 (36.0)

RESULTS

Patient Population

A total of 303 patients taking at least one psychotropic medication presented to the PED for a psychiatric related visit. A total of 100 patients met eligibility criteria (Fig. 1).

Patient demographics are provided in Table 1 according to medication congruency (ie, no GDI vs moderate/significant GDI). The median age of both groups was 14 years (interquartile range [IQR], 5). More males than females (56% vs 44%) were enrolled in the study. Twenty-five percent of the samples were African American, and most patients (93%) identified as non-Hispanic/Latino (Table 1). The 5 most common reasons for PED visit are included in Table 1. Overall, more patients were on incongruent medications (73%) than congruent medications (27%). No significant demographic differences were observed between the 2 groups.

Patient Outcomes

The average CGI-I score was lower (indicating improvement) for those who were on congruent medications (3.37) compared

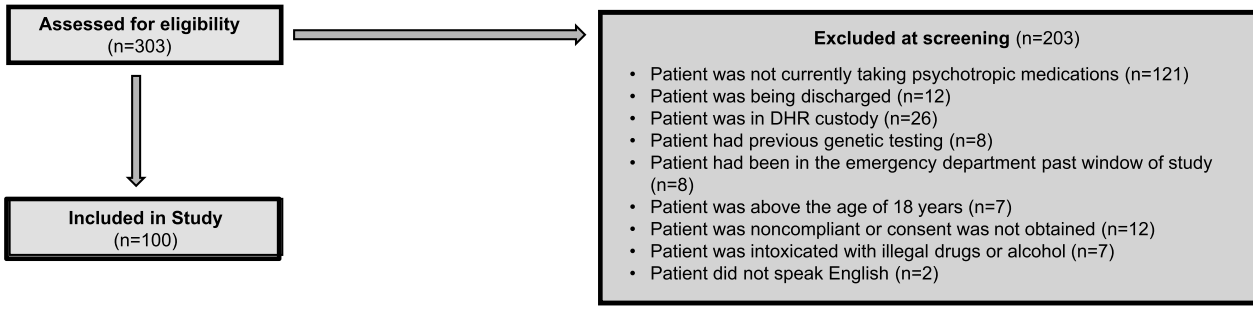

FIGURE 1. Patient enrollment diagram.

with those on incongruent medications (3.68); however, this was not statistically significant ($P = 0.343$; Fig. 2). Among patients who presented for depression, those taking an incongruent medication had a significantly higher CGI-I score (indicating less improvement) compared with those taking only congruent medications (4.1 vs 3.1, $P = 0.036$). Similarly, among patients who presented for suicidal ideation, those who were taking an incongruent medication had a significantly higher CGI-I score than those taking a congruent medication (3.9 vs 3.0, $P = 0.018$; Fig. 2).

Medication Blood Levels

Blood levels were analyzed for escitalopram (n = 10), fluoxetine (n = 10), aripiprazole (n = 15), and clonidine (n = 11). The frequency of psychotropic and ADHD medications prescribed and the number of patients who had blood drug levels analyzed is provided in Supplemental Table 1, http://links.lww.com/PEC/B46. Weight, age, race/ethnicity, and sex were all evaluated according to concentration/dose for each of the 4 medications to determine impact on medication metabolism (Supplemental Fig. 1, http://links.lww.com/PEC/B46). Only escitalopram was found to have a significant difference according to weight ($P = 0.02$; Supplemental Fig. 1, http://links.lww.com/PEC/B46). Patients with a higher weight had lower blood levels of escitalopram. All other demographic characteristics were not significantly associated with medication blood levels.

Medication blood levels were analyzed according to GDIs that included pharmacokinetic, but not pharmacodynamic genes, and predicted change in metabolism (Fig. 3). There was a significant difference between medication blood levels across GDI categories for aripiprazole ($P = 0.01$). Six patients with decreased metabolism had significantly higher levels compared with patients with no GDI/unknown impact on metabolism, whereas 2 patients with increased metabolism were not significantly different from those with no/unknown impact on metabolism (Fig. 3A). Similarly, there was a significant difference between medication blood levels across GDI categories for escitalopram ($P = 0.01$; Fig. 3B). Four patients with decreased metabolism had significantly higher levels compared with patients who had no GDI/unknown impact on metabolism, whereas one patient with increased metabolism

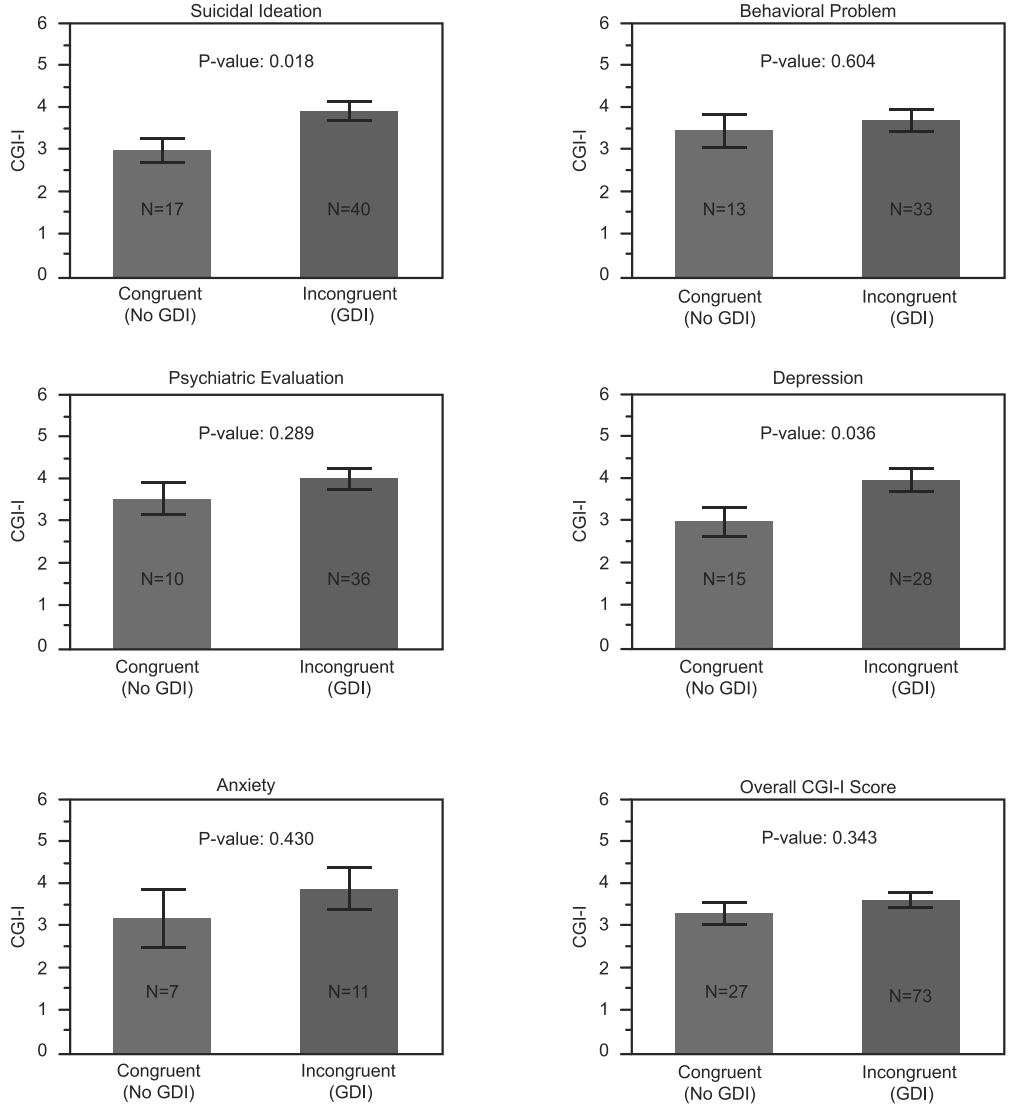

FIGURE 2. Mean CGI-I score based on reason for admission to the pediatric emergency department in patients on incongruent versus congruent medications. Error bars represent ± standard errors of the mean.

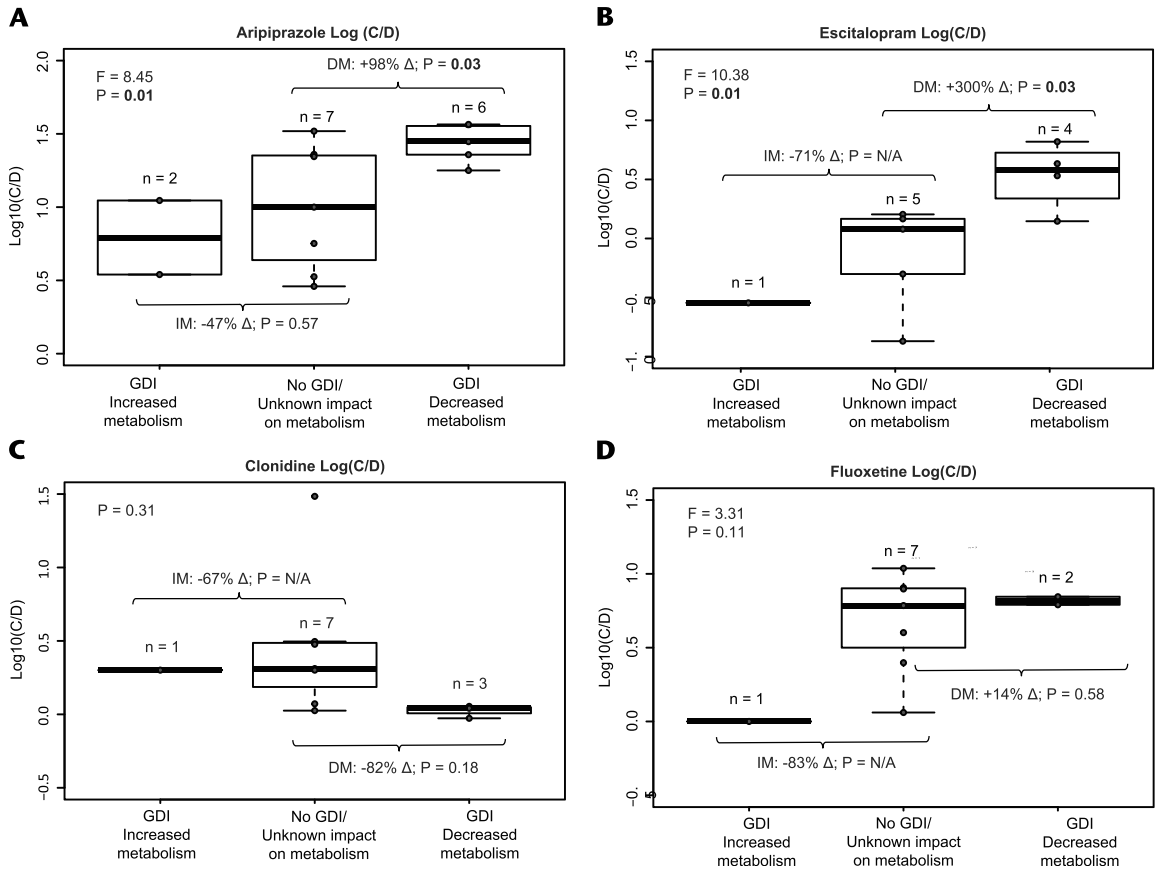

FIGURE 3. Gene-drug interaction and impact on metabolism for each medication type. IM, increased metabolism; DM, decreased metabolism.

was not different from those with no GDI/unknown impact on metabolism. In contrast, there was no significant difference in blood levels between GDI categories for clonidine ($P = 0.31$; Fig. 3C) or fluoxetine ($P = 0.11$; Fig. 3D).

DISCUSSION

The ability of the CPGx test to predict clinical outcomes and medication blood levels in psychiatric settings has been previously reported in adults with depression.[16–19] To date, reports in pediatric patients with depression and other psychiatric conditions have been mixed. The preliminary findings presented here demonstrate that patients taking medications categorized as congruent by the CPGx test had greater relative improvements (numerically) compared with those taking incongruent medications, although differences were not statistically significant across all psychiatric conditions assessed. In addition, significant differences were observed in medication blood levels between GDI categories for aripiprazole and escitalopram. These results are consistent with reports in adults; however, larger, intervention-based studies in pediatric populations will be needed to confirm these findings.

Although numeric improvements in CGI-I score were observed in patients taking congruent medications compared with those taking incongruent medications, this difference was not statistically significant. In patients who presented to the PED with depression and/or suicidal ideation, significantly lower CGI-I scores were observed in patients taking congruent medications compared with those who were taking incongruent medications. In addition, a significant difference between medication blood levels across GDI categories was observed for aripiprazole and escitalopram, but not for fluoxetine and clonidine. It is possible that the sample size in this preliminary study was too small to consistently detect significant differences across all psychiatric conditions and medications; nonetheless, these findings suggest that CPGx testing has the potential to benefit pediatric patients with depression and/or suicidal ideation.

To our knowledge, studies evaluating the association between CPGx testing and patient outcomes in pediatric patients across multiple psychiatric conditions have not yet been performed. However, our findings align with a recent retrospective study that demonstrated improved outcomes after CPGx testing in children and adolescents with depression and anxiety.[23] In contrast, a randomized controlled trial in adolescents with major depressive disorder found no improvement associated with CPGx testing.[22] Although it is possible that CPGx testing may not have clinical utility in adolescents with major depressive disorder, the authors point out that the impact of CPGx testing could have been diluted by patients in the control arm who were incidentally prescribed congruent medications (ie, medications without a GDI). Additional analyses that control for medication congruency will be important to appropriately assess the clinical utility of CPGx testing in this population.

The design and methodology of the present study provided an opportunity to efficiently obtain a preliminary account of clinical improvement and blood levels associated with CPGx testing in the PED pediatric population. Although it is difficult to draw meaningful conclusions from a small sample size, these findings are consistent with larger cohorts in adult patients with depression.[16–21,31] Although larger, more methodologically complex studies in this area are needed, the findings presented

here demonstrate the validity of CPGx testing in pediatric patients for 2 medications, and a potential clinical benefit for determining medication congruency through testing, particularly in pediatric patients with depression and/or suicidal ideation.

Prior literature has shown that finding the appropriate dose for pediatric patients can be challenging. In some cases, children may be underdosed, which can result in failure to respond to a prescribed medication, particularly in poor metabolizers.[10] In the present study, it was not possible to determine whether patients were overdosed or underdosed based on the blood level data because there are insufficient blood-drug reference ranges for pediatric populations. However, there were a substantial number of patients taking incongruent medications, indicating that regardless of the dosing, clinically actionable GDIs occur in this population. Genetic determinants of drug metabolism and receptor binding can be responsible for drug failure and adverse drug reactions. These variations represent the need to predict patient blood levels to reduce potential medication failure resulting from GDIs. Because the number of pediatric patients who are being treated for psychiatric disorders has continued to rise, the use of CPGx testing to personalize treatment might be beneficial, especially for those who are being treated for depression and for those presenting in crisis to a PED.

There are several limitations in the current study. This was a cross-sectional pilot study in a single PED, and no further outcome data were obtained. Therefore, the impacts of GDIs on long-term outcomes of the patients involved in the study are unknown. Future studies including intervention-based methodology will be important to appropriately evaluate the impact of CPGx testing. This study was also limited to pediatric patients presenting to a PED; whether GDIs have an effect on broader groups of pediatric patients is also not known. Because of the design and setting of this study, it was not possible to control for factors that could have impacted medication blood levels, including time since last medication dose, adherence, concomitant medications, and duration of treatment. In addition, data on previous medication trials were not collected. Finally, because this was a preliminary study, the sample size was relatively small.

Research regarding CPGx testing in pediatrics has been limited thus far. Professional societies, such as the American Academy of Child and Adolescent Psychiatry, currently recommend limited use of pharmacogenomic testing and call for continued research to assess the clinical significance of pharmacogenomic testing in the pediatric population.[7] Although more research is needed and this caution is warranted, there is an escalating pediatric mental health crisis in the United States that is overwhelming PEDs and draining limited mental health resources. Psychotropic medication use in the pediatric population can have a profound positive impact on patient outcomes; CPGx testing in pediatric patients who present to the PED during acute crisis may lead to more effective and efficient use of health care resources. The encouraging results presented here support the need for further study in this area.

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