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ARTICLE

# Retrospective Review of Pharmacogenetic Testing at an Academic Children's Hospital

Timothy A. Roberts[1,2,*], Jennifer A. Wagner[2,3], Tracy Sandritter[3], Benjamin T. Black[2,4], Andrea Gaedigk[2,3] and Stephani L. Stancil[1,3]

**There is limited evidence to support pharmacogenetic (PGx) testing in children. We conducted a retrospective review of PGx testing among 452 patients at an academic children's hospital to determine the potential utility of PGx in diseases of childhood and to identify targets for future pediatric pharmacogenetic research. An actionable gene-drug pair associated with the 28 genes tested (Clinical Pharmacogenetics Implementation Consortium (CPIC) level A or B, Pharmacogenomics Knowledge Base (PharmGKB) level 1A or B, or US Food and Drug Administration (FDA) recommendation and a PharmGKB level) was present in 98.7% of patients. We identified 203 actionable gene-drug-diagnosis groups based on the indications for each actionable drug listed in Lexicomp. Among patients with an actionable gene-drug-diagnosis group, 49.3% had a diagnosis where the drug was a therapeutic option and PGx could be used to guide treatment selection. Among patients with an associated diagnosis, 30.9% had a prescription for the actionable drug allowing PGx guided dosing. Three genes (*CYP2C19*, *CYP2D6*, and *CYP3A5*) accounted for all the gene-drug-diagnosis groups with matching diagnoses and prescriptions. The most common gene-drug-diagnosis groups with matching diagnoses and prescriptions were *CYP2C19*-citalopram-escitalopram-depression 3.3% of patients tested; *CYP2C19*-dexlansoprazole-gastritis-esophagitis 3.1%; *CYP2C19*-omeprazole-gastritis-esophagitis 2.4%; *CYP2D6*-atomoxetine-attention deficit hyperactivity disorder 2.2%; and *CYP2C19*-citalopram-escitalopram-obsessive-compulsive disorder 1.5%. PGx could be used to guide selection of current treatment options or medication dosing in almost half (48.7%) of pediatric patients tested. Mood disorders and gastritis/esophagitis are promising targets for future study of PGx testing because of the high prevalence of these diagnoses and associated actionable gene-drug pairs in the pediatric population.**

## Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
☑ There is limited evidence supporting the clinical utility of pharmacogenetic (PGx) testing in children.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
☑ Evaluate the potential clinical utility of PGx testing performed on children to assist with treatment selection and dose adjustment and to identify targets for future research.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**
☑ This study improves our understanding of the potential use of PGx testing in treatment selection and dose adjustment while treating children. Almost half of our patients (47.8%) had a clinical diagnosis where their results could influence treatment and 15.0% were prescribed a medication where their test results could be used to adjust dosing. Three genes (*CYP2C19*, *CYP2D6*, and *CYP3A5*) accounted for all the actionable gene-drug pairs with matching diagnoses and prescriptions. Mood-disorders-selective serotonin reuptake inhibitor and gastroesophagitis-proton pump inhibitors were the most commonly affected diagnosis-drug combinations identified.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**
☑ Results from this study identify areas for future PGx research in children and may guide the development of tailored clinical decision support tools to better serve their needs.

Pharmacogenetic (PGx) testing, specifically the inquiry into genetic variants in pharmacokinetic or pharmacodynamic pathways involved in medication metabolism or response, is commercially available and being promoted to improve patient outcomes.[1] The level of evidence supporting the clinical utility of testing for variants in individual genes differs, and translation of the test results into clinical practice is complicated. Several organizations, including the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group (DPWG), have created detailed, evidence-based, gene-drug clinical

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practice guidelines that can assist providers in applying the results of PGx testing to the management of medications used to treat mood disorders, cardiovascular disease, cancer, or other diseases among adults.[2,3]

Previous research in adult populations has demonstrated the clinical utility[4–8] and cost-effectiveness[9,10] for both reactive PGx testing to guide current treatment and pre-emptive testing to guide future treatment decisions. However, the evidence base for PGx testing in pediatric patients and in treatment of diseases prevalent during childhood is less robust.

Despite the lack of current evidence in favor of PGx implementation for children, enthusiasm for the potential of PGx remains high among pediatric clinicians. A recent survey of pediatric providers in the United States and Japan found that > 80% believe PGx will improve the safety and efficacy of pediatric drug therapy. Findings from this survey endorsed the interest in education to equip pediatric clinicians with the skills to implement PGx.[11] However, the current guidelines for interpreting and implementing PGx are based largely on adult data, and it is unclear how well they apply to the care of children and adolescents. Thus, PGx testing in pediatrics is most often reactive, and it is not clear which pediatric patients may benefit most from reactive testing with regard to their current clinical care or pre-emptive testing to guide future drug therapy.

A previous study of medication use at a children's hospital, identified 10 commonly prescribed medications with evidence-based guidelines for dosing adjustment based on PGx testing results (ondansetron, oxycodone, codeine, omeprazole, lansoprazole, sertraline, amitriptyline, citalopram, escitalopram, and risperidone). Only three of these drugs (codeine, omeprazole, and lansoprazole) had adequate pediatric data in support of age-specific recommendations.[12]

The goal of this study was to describe the proportion of pediatric age patients who may benefit from pre-emptive PGx testing and identify high-impact areas for future research by conducting a retrospective review of the records of patients who had PGx testing performed at Children's Mercy Hospital. We identified (1) actionable gene-drug pairs associated with the genes evaluated at our hospital, (2) clinical diagnostic groups associated with these gene-drug pairs creating gene-drug-diagnosis groups, (3) the proportion of patients who can use PGx testing results to assist with treatment selection for current diagnoses (potentially actionable gene-drug-diagnosis group and a matching clinical diagnosis, (4) the proportion of patients who can use PGx testing results to guide medication dosing (potentially actionable gene-drug-diagnosis group with a matching clinical diagnosis and drug prescription), and (5) the pediatric diagnosis groups with the highest frequency of patients with actionable test results with a matching clinical diagnosis and drug prescription.

## METHODS

This is a retrospective review of PGx testing of pediatric patients conducted between 2017 and 2019 at Children's Mercy Hospital, an academic children's hospital in the midwestern United States. Testing could be obtained by community providers through referral to the Genomic and Ontogeny-Linked Dose Individualization and cLinical Optimization for KidS (GOLDILOKs) Clinic or by Children's Mercy providers ordering the test directly. The hospital used a commercially available, 20-gene PGx panel (OneOme, Minneapolis, MN) for all tests. The specific genes assessed on this panel varied over time, as particular genes were removed and replaced with other genes, so the results from 28 different genes were assessed. When the results of this test were returned to Children's Mercy from the outside laboratory, one of the providers trained in PGx reviewed the results. Then, that provider sent the family and the provider who requested the test an individualized explanation of the results in addition to relevant specific medication guidance. The testing was performed at the discretion of the ordering provider. There was no clinical decision support built into the electronic health record (EHR) based on the results of the PGx testing, and testing was not performed as part of a structured pre-emptive testing program. In addition to PGx test results, we also collected the age, sex, and race/ethnicity for each patient.

To determine both the current and possible future clinical utility of PGx testing in the patients tested, we reviewed the test results from each patient to identify potentially actionable genetic variants with evidence-based guidance for drug therapy (gene-drug pairs). We also identified clinical diagnoses for which the drug guidance can be put into action (gene-drug-diagnosis groups). We defined potentially actionable gene-drug pairs at the allele level as the following: (i) CPIC level A or B guidance, (ii) Pharmacogenomics Knowledge Base (PharmGKB) level 1A or 1B guidance, or (iii) gene-drug pairs with a US Food and Drug Administration (FDA)-approved drug label of "actionable pgx," "genetic testing recommended," or "genetic testing required" and a PharmGKB PGx level. We only searched for guidelines or recommendations associated with the alleles that were present in our sample population. For each actionable gene-drug pair, we identified all FDA-approved and off-label indications for the drug using the Lexicomp medication database if the PGx guidance did not limit treatment recommendations to a specific disease process.[13] Both adult and pediatric indications for medications were included in our study. These indications were subsequently mapped to a specific diagnosis or group of diagnoses and their associated International Classification of Disease-10th edition (ICD-10) codes. We combined the clinical indications and associated diagnoses for each drug with our list of potentially actionable gene-drug pairs to create a list of potentially actionable gene-drug-diagnosis groups. We included both off-label and FDA-approved indications because off-label medication use is a frequent occurrence in pediatric care.[14] We did not include conditions that we were unable to map to a limited set of ICD-10 codes that would make an effective target for pre-emptive PGx testing, such as acute pain or severe nausea.[15] We also did not include drugs where the guidelines available at the time of the study did not provide any dosing recommendations based on PGx test results (e.g., risperidone). We initially included SLC6A4:citalopram/escitalopram in our study as this had a CPIC level of B/C and dosage guidance in

PharmGKB. However, the evidence supporting this dosage guidance was contradictory at the time of our initial review of the CPIC and PharmGKB guidance and has become more unclear over time. Therefore, we elected to remove this gene from our results.

For patients with a potentially actionable gene-drug-diagnosis group, we reviewed our hospital EHR database containing visit data and ICD-10 codes to determine if a patient had a current (within 2 years before or after PGx testing) clinical diagnosis with a condition included in that gene-drug-diagnosis group. For patients with a matching clinical diagnosis, we reviewed the EHR database to determine if the patient had a prescription documented in the EHR for the drug included in that gene-drug-diagnosis group. See **Figure 1** for an overview of our analytic strategy.

Exclusion of medications to treat potential future acute pain or severe nausea will likely underestimate the potential benefits of PGx in general. We attempted, however, to estimate the number of patients per year seen at Children's Mercy Kansas City who may benefit from PGx testing prior to receiving a prescription for ondansetron, codeine, or oxycodone. First, we determined the number of unique patients prescribed these medications at Children's Mercy, Kansas City, between April 1, 2018, and March 31, 2019. Then, this number was multiplied by the proportion of patients in our sample with actionable PGx results associated with these drugs. We did not review individual patient notes and attempt to infer the provider's intent when ordering the PGx testing or how the results were incorporated into the patient's medical care as this was outside the scope of our study. This study was approved by the Children's Mercy Kansas City Institutional Review Board.

## RESULTS

PGx test results were available for 452 patients. The average age of our patients was 11.9 ± 4.3 years, 51.8% were boys, and 79.1% were white, 9.9% of African descent, 2.6% Hispanic/Latino, 1.8% Asian, 0.7% American Indian, and 0.7% Hawaiian or Pacific Islander. Ordering services included individualized therapeutics/clinical pharmacology, behavioral health, and adolescent medicine (**Table 1**).

### Gene-drug pairs

We identified one or more guidelines or recommendations for drug management associated with 16 of the 28 genes tested on the commercial PGx panel. These guidelines describe a total of 78 potentially actionable gene-drug pairs associated with the alleles identified by the PGx test. In our sample, 446 of 452 patients (98.7%) tested had at least one potentially actionable gene-drug pair (**Table 2**). The most common gene-drug pairs identified were *VKORC1*-warfarin with 266 actionable results out of 452 tests (58.8%), *IFNL4*-peginterferon alfa-2b 170 of 292 tests (58.2%), *CYP4F2*-warfarin 83 of 187 tests (44.4%), *CYP2C19*-dexlansoprazole 148 of 452 tests (32.7%), and *CYP2C19*-clopidogrel 148 of 452 tests (32.7%).

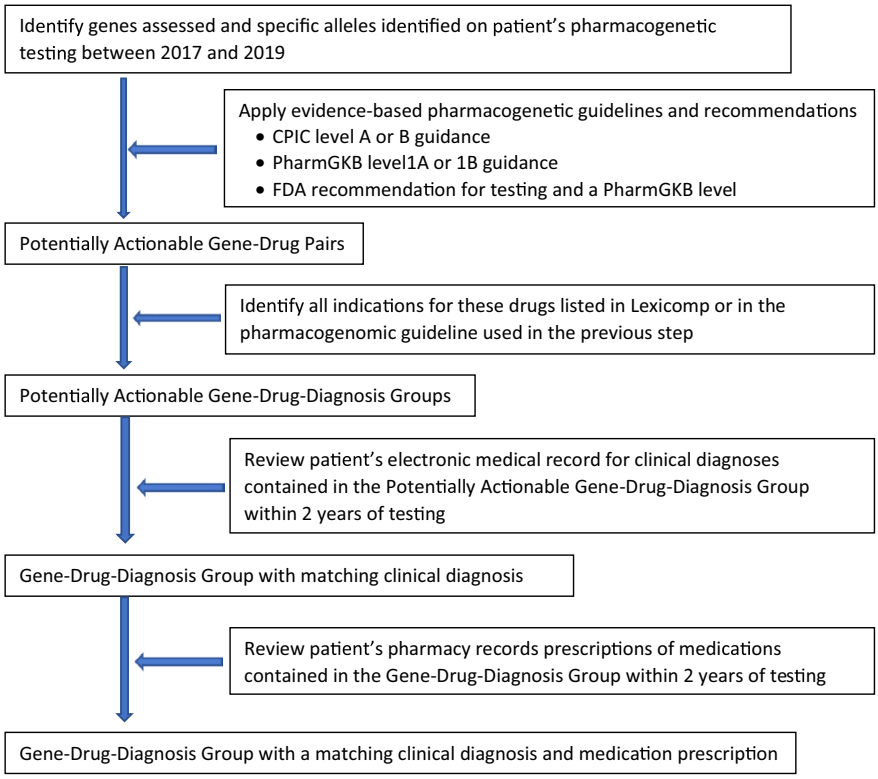


**Figure 1** Interpretation of pharmacogenetic test results. CPIC, Clinical Pharmacogenetics Implementation Consortium; FDA, US Food and Drug Administration; PharmGKB, Pharmacogenomics Knowledge Base.

**Table 1 Study demographics**

| Demographic group | Mean ± SD |
|---|---|
| Age, years | 11.9 ± 4.3 |
| Sex | % of total |
| Female | 48.2% |
| Male | 51.8% |
| Race/ethnicity | |
| White | 79.1% |
| Black/African American | 9.9% |
| Hispanic/Latino | 2.6% |
| Asian | 1.8% |
| Native American | 0.7% |
| Pacific Islander | 0.7% |
| Unknown | 5.3% |

### Gene-drug-diagnosis groups

Combining the potentially actionable drug-gene pairs with the associated FDA-approved and off-label indications for the drugs produced 203 gene-drug-diagnosis groups (e.g., *CYP2C19*-citalopram/escitalopram-depression). See **Table S1** for details of the gene-drug-diagnosis groups identified and related ICD-10 codes. In our sample, the median number of potentially actionable gene-drug-diagnosis groups per patient was 20, with a range of 0–109.

### Matching clinical diagnoses among patients with a potentially actionable gene-drug-diagnosis group

The PGx test results were informative for treatment selection for current diagnoses among 220 of the 452 patients (48.7%) tested (actionable gene-drug-diagnosis group with a matching diagnosis). Ten genes accounted for the gene-drug-diagnosis pairs in these patients (**Table 2**). The most common matching clinical diagnosis among patients with a potentially actionable gene-drug-diagnosis group was attention deficit-hyperactivity disorder (ADHD). Of the 193 patients with a gene-drug-diagnosis group that included ADHD, 121 (62.7%) had a matching clinical diagnosis of ADHD. Other common conditions with actionable gene-drug-diagnosis groups and matching clinical diagnoses included: anxiety disorders 89 of 183 (48.6%), depressive disorders 56 of 183 (30.6%), and gastritis/esophagitis/ulcer disease 56 of 263 (21.3%).

### Exposure to actionable medications among patients with a potentially actionable gene-drug-diagnosis group and a matching clinical diagnosis

The PGx results could be used to adjust the dosing of at least one currently prescribed drug among 68 of the 452 patients (15.0%) tested. Two or more potentially actionable gene-drug-diagnosis groups with a matching clinical diagnosis and drug prescription within 2 years of testing were present in 22 of 452 patients (4.9%) tested. Three genes accounted for all the gene-drug pairs involved in this group (*CYP2C19*, *CYP2D6*, and *CYP3A5*; **Table 3**). The most common gene-drug-diagnosis groups with a matching clinical diagnosis and prescription among the 452 patients tested were *CYP2C19*-citalopram, escitalopram-depression 3.3% (*n* = 15); *CYP2C19*-dexlansoprazole-gastritis-esophagitis 3.1% (*n* = 14); *CYP2C19*-omeprazole-gastritis-esophagitis

**Table 2 Frequency of actionable PGx test results**

| Gene | Percentage of patients tested with an actionable gene-drug pair | Percentage of patients tested where PGx results are useful for treatment of current disease[a] | Percentage of patients tested where PGx results are useful for dosing of currently prescribed drugs[b] |
|---|---|---|---|
| *CYP2C19* | 62.3 | 32.9 | 11.0 |
| *CYP2D6* | 19.6 | 17.0 | 4.9 |
| *CYP3A5* | 22.9 | 0.7 | 0.2 |
| *HLA-A* | 5.2 | 2.6 | 0.0 |
| *CYP2C9* | 24.9 | 1.3 | 0.0 |
| *SLCO1B1* | 27.1 | 1.1 | 0.0 |
| *TPMT* | 9.5 | 0.7 | 0.0 |
| *VKORC1* | 58.8 | 0.4 | 0.0 |
| *UGT1A1* | 11.0 | 0.2 | 0.0 |
| *NUDT15* | 2.2 | 0.2 | 0.0 |
| *IFNL4* | 58.9 | 0.0 | 0.0 |
| *CYP4F2* | 44.0 | 0.0 | 0.0 |
| *HLA-B* | 9.5 | 0.0 | 0.0 |
| *F5* | 5.1 | 0.0 | 0.0 |
| *CYP2C rs12777823* | 3.4 | 0.0 | 0.0 |
| *DPYD* | 2.0 | 0.0 | 0.0 |

*HLA-A* alleles assessed: *31:01; *HLA-B* alleles assessed: *15:02, *57:01 and *58:01.
*COMT*, *CYP1A2*, *CYP2B6*, *CYP3A4*, *DRD2*, *F2*, *GRIK4*, *HTR2A*, *HTR2C*, *IL28B*, *OPRM1*, and *SLC6A4* genotypes were available on some patients as well, but no evidence-based guidelines for the interpretation of these results were identified that met our inclusion criteria.
PGx, pharmacogenetic.
[a]Patient has ≥ 1 actionable gene-drug-diagnosis group and a matching clinical diagnosis within 2 years of testing. [b]Patient has ≥ 1 actionable gene-drug-diagnosis group, a matching clinical diagnosis, and a matching drug prescription within 2 years of testing.

Table 3 Actionable gene-drug-diagnosis groups with a matching clinical diagnosis and medication prescription (***n*** = 452)

| Gene | Genotype predicted phenotype | Drugs | Diagnosis | Actionable gene-drug-diagnosis group (% of all tested) | PGx results are useful for treatment of current disease (% of all tested)[a] | PGx results are useful for dosing of currently prescribed drugs (% of all tested)[b] |
|---|---|---|---|---|---|---|
| *CYP2C19* | UM (**17/*17*)<br>UM/RM (**1/*17*)<br>PM (**2/*2*, **2/*3*) | Citalopram, escitalopram | Depression | 125 (27.7) | 34 (7.5) | 15 (3.3) |
| | | | Obsessive compulsive disorder | 125 (27.7) | 22 (4.9) | 7 (1.5) |
| | | | Anxiety disorders | 125 (27.7) | 14 (3.1) | 3 (0.7) |
| | | Citalopram | Dementia | 125 (27.7) | 1 (0.2) | 1 (0.2) |
| | | Escitalopram | Autism | 125 (27.7) | 34 (7.5) | 1 (0.2) |
| | | Clomipramine, doxepin, imipramine | Anxiety disorders | 125 (27.7) | 82 (18.1) | 3 (0.7) |
| | | Amitriptyline, doxepin | Insomnia | 125 (27.7) | 29 (6.4) | 3 (0.7) |
| | | Imipramine | ADHD | 125 (27.7) | 76 (16.8) | 2 (0.4) |
| | | | Enuresis | 125 (27.7) | 8 (1.8) | 1 (0.2) |
| | | Amitriptyline | Migraine headache | 125 (27.7) | 3 (0.7) | 1 (0.2) |
| | | Pantoprazole | Gastritis, esophagitis, and ulcers | 125 (27.7) | 23 (5.1) | 6 (1.3) |
| | IM (**1/*2*, **1/*3*, **1/*4*, **2/*17*)<br>PM (**2/*2*, **2/*3*) | Dexlansoprazole | Gastritis, esophagitis, and ulcers | 148 (32.7) | 34 (7.5) | 14 (3.1) |
| | UM (**17/*17*)<br>UM/RM (**1/*17*) | Omeprazole | Gastritis, esophagitis, and ulcers | 115 (25.4) | 22 (4.9) | 11 (2.4) |
| | PM (**2/*2*, **2/*3*) | Lansoprazole | Gastritis, esophagitis, and ulcers | 10 (2.2) | 1 (0.2) | 1 (0.2) |
| | | Sertraline, diazepam | Anxiety disorders | 10 (2.2) | 8 (1.8) | 3 (0.7) |
| | RM (**1/*17*)<br>PM (**2/*2*, **2/*3*) | Amitriptyline | Tension headache | 95 (21.0) | 16 (3.5) | 1 (0.2) |

(Continues)

**Table 3 (Continued)**

| Gene | Genotype predicted phenotype | Drugs | Diagnosis | Actionable gene-drug-diagnosis group (% of all tested) | PGx results are useful for treatment of current disease (% of all tested)[a] | PGx results are useful for dosing of currently prescribed drugs (% of all tested)[b] |
|---|---|---|---|---|---|---|
| *CYP2D6* | UM (*(*1/*2A)xN, *1/*1x2, *1/*1xN, *1/*35x2, *2AxN/*2AxN, *2AxN/*41*)<br>IM (*(*4/*10)xN, *3/*17, *10+*36/*10+*36, *3/*41, *3/*9, *4/*9, *4+*68/*9, *4/*10, *4/*29, *4/*41, *4+*4N/*41, *5/*9, *5/*10+*36, *5/*17, *5/*41, *5/*59, *6/*10, *6/*41*)<br>PM (*(*4/*4)xN, *3/*4, 3/*6, *4/*4, *4/*4+*68, *4/*5, *4/*6, *5/*68*) | Amitriptyline, venlafaxine | Recurrent headache | 76 (16.8) | 19 (4.2) | 6 (1.3) |
| | | Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine, venlafaxine | Depression | 76 (16.8) | 25 (5.5) | 5 (1.1) |
| | | Clomipramine, venlafaxine | Obsessive compulsive disorder | 76 (16.8) | 16 (3.5) | 3 (0.7) |
| | | Desipramine, imipramine, nortriptyline, venlafaxine | ADHD | 76 (16.8) | 47 (10.4) | 2 (0.4) |
| | | Amitriptyline, doxepin | Insomnia | 76 (16.8) | 15 (3.3) | 2 (0.4) |
| | | Imipramine, venlafaxine | Autism | 76 (16.8) | 20 (4.4) | 1 (0.2) |
| | | Clomipramine, doxepin, imipramine, venlafaxine | Anxiety disorders | 76 (16.8) | 6 (1.3) | 1 (0.2) |
| | NM (**1/*10, *2A/*10+*36x2, *2A/*10*)<br>IM (**10/*10, *10/*29, *10/*41, *10+*36/*10+*36, *3/*9, *3/*17, *3/*41, *4/*9, *4+*68/*9, *4/*10, (*4/*10)xN, *4/*29, *4/*41, *4+*4N/*41, *5/*9, *5/*10+*36, *5/*17, *5/*41, *5/*59, *6/*10, *6/*41*)<br>PM (*(*4/*4)xN, *3/*4, *3/*6, *4/*4, *4/*4+*68, *4/*5, *4/*6, *5/*68*) | Atomoxetine | ADHD | 82 (18.1) | 50 (11.1) | 10 (2.2) |
| | IM (**10/*10, *10/*29, *10/*41, *10+*36/*10+*36, *3/*9, *3/*17, *3/*41, *4/*9, *4+*68/*9, *4/*10, (*4/*10)xN, *4/*29, *4/*41, *4+*4N/*41, *5/*9, *5/*10+*36, *5/*17, *5/*41, *5/*59, *6/*10, *6/*41*)<br>PM (*(*4/*4)xN, *3/*4, *3/*6, *4/*4, *4/*4+*68, *4/*5, *4/*6, *5/*68*) | Pimozide | Tourette disorder | 70 (15.5) | 11 (2.4) | 2 (0.4) |
| | IM (**5/*10+*36*)<br>PM (**3/*6, *4/*4, (*4/*4)xN, *4/*4+*68, *4/*5, *4/*6, *5/*68*) | Aripiprazole, brexpiprazole | Depression | 30 (6.6) | 11 (2.4) | 1 (0.2) |
| *CYP3A5* | NM (**1/*1*)<br>IM (**1/*3, *1/*6, *1/*7*) | Tacrolimus | Organ transplant | 103 (22.8) | 1 (0.2) | 1 (0.2) |

The remaining 183 gene-drug-diagnosis groups did not have any patients taking a related medication.
Only genotypes that were observed among the cases in our study are listed. Other genotypes (not represented) are likely to be observed in other patient populations.
Predicted phenotypes are based on genotype as listed on the OneOme report supplemented by information on the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogenomics Knowledge Base (PharmGKB) websites.
ADHD, attention deficit hyperactivity disorder; IM, intermediate metabolizer; NM, normal metabolizer (previously referred to as EM, extensive metabolizer); PGx, pharmacogenetic; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolize.[36]
Genotypes listed in parentheses (e.g., *(*4/*4) × N*) indicate the presence of a gene duplication or multiplication on one or both of the alleles.
*CYP* star allele nomenclature is according to the Pharmacogene Variation Consortium (pharmvar.org).[37,38]
[a]Patient has ≥ 1 actionable gene-drug-diagnosis group and a matching clinical diagnosis within 2 years of testing.
[b] Patient has ≥ 1 actionable gene-drug-diagnosis group, a matching clinical diagnosis, and a matching drug prescription within 2 years of testing.

2.4% (*n* = 11); *CYP2D6*-atomoxetine-ADHD 2.2% (*n* = 10); and *CYP2C19*-citalopram, escitalopram-obsessive-compulsive disorder 1.5% (*n* = 7).

### Potential benefit of PGx testing in the treatment of acute pain or severe nausea

CYP2D6 ultrarapid metabolizers are at risk for treatment failure when given ondansetron to treat severe nausea. We estimate that 1,227 of the 18,492 patients a year (6.6%) prescribed ondansetron at Children's Mercy are at risk for treatment failure and could benefit from PGx testing to allow selection of an alternative antinausea medication. CYP2D6 ultrarapid metabolizers are also at risk for respiratory depression when treated with oxycodone. We estimate that ~ 689 of the 10,382 patients a year (6.6%) prescribed oxycodone at Children's Mercy could benefit from PGx testing to allow selection of an alternative analgesic. Likewise, ~ 4 of the 46 patients a year (8.4%) prescribed codeine could benefit from PGx testing.

## DISCUSSION

Providers could use PGx test results to guide treatment for current diseases in over half of the pediatric patients in our study and to adjust medication dosing in 15% of the patients tested. Most matching diagnoses and drug prescriptions were found among pediatric patients diagnosed with mental health conditions or esophagitis-gastritis. These two diagnostic groups emerged as the main targets for pre-emptive testing in children prior to selecting a treatment option or prescribing medication to treat these conditions.

### Results in context with previous literature

The frequency of actionable genetic variants in our study was similar to the frequency seen in previous studies of adult patients.[16–18] This suggests that the underlying genetic diversity in our sample was similar to previous samples.

Our study identified many of the same medications (omeprazole, lansoprazole, sertraline, amitriptyline, citalopram, and escitalopram) as a previous study of pediatric age patients.[12] The commonly used medications in one of these studies that we did not identify were specifically excluded from our analysis because we could not map the indications for these drugs, pain and nausea, to a specific set of ICD-10 codes (ondansetron, oxycodone, and codeine) or because the available guidelines did not provide any guidance on dose modification based on the test results (e.g., risperidone). Thus, our findings provide conservative evidence of the potential clinical utility of PGx testing for conditions outside of acute pain and nausea. We estimate that the inclusion of these broad conditions would increase the apparent benefit PGx testing among pediatric patients. However, identifying and providing pre-emptive screening to all patients who might experience future severe nausea or acute pain would be logistically challenging. On the other hand, providers who anticipate that their particular patient is at high risk for these conditions should consider PGx testing and include the results in clinical decision support tools to help guide future treatment. Another study examined medication use among children and adults to identify patient populations that would benefit from PGx testing. Like our study, this study identified child mental health as one of the clinical areas most likely to benefit from PGx testing.[19] Our investigation expands on this previous study by examining the potential clinical utility of PGx testing in treatment selection and dose adjustment among pediatric patients by identifying the frequency of matching diagnoses and prescriptions in pediatric patients with a potentially actionable gene-diagnosis-drug combination.

Although our sample was taken from a select group of patients referred for PGx testing, the immediate clinical utility of the results in our sample was similar to those seen in previous studies of adults and exceeded that reported in pediatric studies. In a study of Chinese children, up to 9% of patients received at least one medication associated with a CPIC guideline.[20] In a study comprising 600 adult patients seen in outpatient or perioperative cardiology clinics and another studying 122 patients with cardiac catheterization, 16.1% and 20% of patients, respectively, were identified to have a PGx variant that may affect the metabolism of a currently taken medication.[21–22] When exposure inquiry was expanded to medication use in the past 20 years, 80% of English adults had exposure to at least 1 drug with PGx guidance.[23] This compares to the 15% (68/452) of pediatric patients in our study who had a matching prescription within 2 years before or after PGx testing. Taken together, our results augment current knowledge of the clinical utility of PGx testing in various populations and quantifies the potential impact in pediatric patients.

### Communicating testing results to pediatric age patients and families

Almost all the patients in our sample had a potentially actionable genetic variant. However, only 48.7% had a diagnosis where this information could be clinically useful to current care. For example, of the 452 patients tested, 58.8% had variants of *VKORC1* and 44.0% had variants of *CYP4F2* that influence warfarin dosing requirements. However, only two of these patients had a clinical diagnosis for which warfarin was a therapeutic option, and neither of them had been prescribed warfarin within 2 years of testing.

Describing how "actionable" test results can influence current care and might affect future care in certain circumstances contributes to the complexity of returning PGx results to pediatric patients and their families. Other factors contributing to this complexity include emerging evidence for the possible discordance between adults and children of PGx impact in the setting of obesity.[24] While discussing PGx results, providers need to discuss the impact of test results on current treatment decisions and acknowledge uncertainty when evidence is lacking. Providers also need to discuss test results that do not apply to the patient's care but need to be preserved in case the results become relevant in the future. Providers also need to be mindful that they do not create additional problems for the child while delivering this information. Parental perception that their child is "abnormal" or has a special susceptibility to problems can result in the vulnerable child syndrome.[25] In this syndrome, unwarranted parental anxiety about a

real or perceived illness in a child can change parental behavior causing increased health care utilization, increased anxiety in the child, and limit development of autonomy. Interventions to facilitate discussions of test results and assess provider, patient, and parent understanding of the results would be a valuable area of future research. In addition, studies that examine the risk of increased parental perception of child vulnerability associated with abnormal results against the benefit of providing PGx guidance that applies primarily to diseases prevalent among adults would be beneficial. This is especially true in younger children when the PGx guidance refers to a disease the child is unlikely to have for another 40–50 years, such as breast cancer, and treatment options for that disease which will probably be irrelevant at that point.

### Potential high-yield medical conditions for pediatric PGx research

Our study revealed that the majority of currently actionable PGx test results are restricted to a small number of genes, thus highlighting the high-impact, priority areas that should be prioritized in future PGx research endeavors with children. Gastritis/esophagitis/ulcer disease, and mental health disorders were the most frequently identified disorders involved in actionable gene-drug-diagnosis groups. These conditions are common problems in pediatric populations, with these gastrointestinal conditions affecting 4.4%, mood disorders affecting 4.2%, and attention deficit disorder/ADHD affecting 8.6% of children and adolescents.[26,27]

There is also some evidence demonstrating the relevance of PGx testing in the treatment of these conditions in children. CYP2C19 is the enzyme responsible for metabolizing many drugs (e.g., proton pump inhibitors (PPIs) like omeprazole, dex/lansoprazole) prescribed for the treatment of gastritis/ulcer disease. Evidence linking *CYP2C19* genotype-predicted phenotype and PPI adverse events in young children (0–3 years) as well as PPI responsiveness suggests the relevance of this PGx relationship in the pediatric population.[28,29] A recent simulation study linked *CYP2C19* genotype-predicted phenotype with altered systemic exposure of the selective serotonin reuptake inhibitors, es/citalopram and sertraline, in children and adolescents. Dose modifications based on genotype-predicted phenotype (i.e., PGx variation) were suggested, but this has yet to be evaluated prospectively.[30] Other studies have found associations among *CYP2C19* genotype-predicted phenotype and tolerability, adverse events, and time to selective serotonin reuptake inhibitor response among children.[31,32] Last, *CYP2D6* genotype has been associated with response to psychiatric medications in adults but this has not been confirmed in pediatric patients.[33]

Prospective trials of PGx in pediatrics are needed to confirm that the genotype-predicted phenotype relationships seen in adults are applicable in children and determine the impact of PGx-guided treatment on disease outcomes. The relationship of *SLCO1B1* genotype and simvastatin acid systemic exposure in adults vs. children is a salient example. The impact of *SLCO1B1* genotype is greater than twofold higher in children compared with that reported in adults.[34] Interestingly, although this was appreciated for simvastatin, but no appreciable differences were evident for its classmate pravastatin underscoring the importance of specific gene-drug inquiries.[35] Careful consideration regarding measures of efficacy, tolerability, and drug retention is imperative to produce evidence that is translatable to the bedside.

### Study limitations

Advantages of this study include our focus on a pediatric population and correlation of PGx testing results with the frequency of diseases and medication use among the patients tested. However, this study has several limitations. We obtained our sample from a group of patients referred to an academic children's hospital that may have a higher burden of disease and thus may not represent the larger population of patients in the community. However, the prevalence of actionable genetic variants in our population mirrors that of adult literature, decreasing this concern about our sample.[16] The results from our study may not apply to different pediatric healthcare systems with different specialty clinics or referral patterns. We only examined guidance that contained genotypes included on the commercial PGx panel used at our institution. A panel that assessed different genes or a larger variety of genotypes would produce different results and might demonstrate a greater benefit of PGx in pediatric patients. Our findings regarding diagnoses and prescriptions were limited to those contained within our hospital's EHRs. Diagnoses and prescriptions not documented in the EHR would not be captured, and neither would medications for indications that are not FDA-approved or present in the Lexicomp. Therefore, our findings may underestimate the prevalence of relevant diagnoses and medication use in this population. In addition, we did not include medications used to treat the symptoms of acute pain and severe nausea (oxycodone, codeine, and ondansetron) in our analytic strategy. However, we estimated how many patients may benefit per year from PGx prior to using these medicines by examining the number of prescriptions for these medications and rates of actionable gene-drug pairs in our sample. It remains unknown though how many of these prescriptions were first-time prescriptions and how many were follow-ups of previous prescriptions. Patients who had taken these medicines previously and found them effective and without side effects would be at much lower risk of having an underlying actionable PGx variant. Therefore, our method of estimation may overestimate the benefit of PGx testing associated with these medications. Given the retrospective nature of this study and limitations related to available clinical documentation within the EHR, we were unable to determine the impact of PGx testing on provider and family decision making. Future studies in pediatrics may consider exploring patients' health care and medication use before and after testing, association of test results with patients' experience of treatment efficacy and side effects, providers' understanding of the PGx test results, and the influence of dosing guidelines on provider dosing practices.

## CONCLUSION

Most children in our study had PGx variants that could impact their current treatment. Most of these acutely relevant findings were limited to three genes (e.g., *CYP2D6*, *CYP2C19*, and *CYP3A5*) and two major diagnosis groups (e.g., mental health disorders and gastritis/esophagitis/ulcer disease). Mental health disorders and gastritis/esophagitis/ulcer disease are prime targets for future study of PGx testing because of the high prevalence of these diagnoses and actionable gene-drug-diagnostic groups in children and adolescents. Considerations for future work also include the development of targeted pediatric PGx panels for dissemination in primary care that eliminate genes without any evidenced-based guidelines or recommendations for drug management, for example, *COMT*, *DRD2*, *GRIK4*, *HTR2A*, *HTR2C*, *IL28B*, *OPRM1*, and SLC6A4, or are associated with drugs rarely used in children and adolescents (such as *IFNL4*-peginterferon alfa-2b). Limiting the number of genes tested may reduce complexity for the general practitioner in interpreting/returning results to patients and families. Development of a targeted pediatric PGx panel should ideally be informed by a cost:benefit analysis when determining which evidence-based genes to omit (e.g., cost of repeat PGx testing at a later date and parental anxiety) balanced with the benefits of pre-emptive testing to assist with diseases that might occur 40–50 years in the future. Through future study of the impact of PGx testing on patient outcomes and the optimal delivery of PGx findings to patients and families, we will learn how best to use this important tool to implement and practice precision medicine in pediatric patients.

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