



SPECIAL ARTICLE

Perspectives from the Society for Pediatric Research: pharmacogenetics for pediatricians

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This review evaluates the pediatric evidence for pharmacogenetic associations for drugs that are commonly prescribed by or encountered by pediatric clinicians across multiple subspecialties, organized from most to least pediatric evidence. We begin with the pharmacogenetic research that led to the warning of increased risk of death in certain pediatric populations (“ultrarapid metabolizers”) who are prescribed codeine after tonsillectomy or adenoidectomy. We review the evidence for genetic testing for thiopurine metabolism, which has become routine in multiple pediatric subspecialties. We discuss the pharmacogenetic research in proton pump inhibitors, for which clinical guidelines have recently been made available. With an increase in the prevalence of behavioral health disorders including attention deficit hyperactivity disorder (ADHD), we review the pharmacogenetic literature on selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and ADHD medications. We will conclude this section on the current pharmacogenetic data on ondansetron. We also provide our perspective on how to integrate the current research on pharmacogenetics into clinical care and what further research is needed. We discuss how institutions are managing pharmacogenetic test results and implementing them clinically, and how the electronic health record can be leveraged to ensure testing results are available and taken into consideration when prescribing medications.

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IMPACT:

- While many reviews of pharmacogenetics literature are available, there are few focused on pediatrics.
- Pediatricians across subspecialties will become more comfortable with pharmacogenetics terminology, know resources they can use to help inform their prescribing habits for drugs with known pharmacogenetic associations, and understand the limitations of testing and where further research is needed.

INTRODUCTION

Pharmacogenetics is an emerging component of precision medicine. Many medications prescribed by pediatricians and pediatric subspecialists are influenced by pharmacogenetic variants. Yet, few pediatricians have the training to incorporate pharmacogenetic results into practice. This review will provide an overview of pharmacogenetics, review pharmacogenetic research for exemplary gene–drug pairs, discuss clinical implementation, and provide a general perspective for the field.

DEFINITION OF KEY TERMS AND RESOURCES

Discussion of pharmacogenetic literature is facilitated by the knowledge of key terms and resources (Table 1).^{1–5} While the terms *pharmacogenetics* and *pharmacogenomics* are often used interchangeably, pharmacogenetics is the study of single genes and their effect on drug response, and pharmacogenomics is focused on how the entire genome influences drug response. Some pharmacogenes affect drug absorption, distribution, metabolism, or excretion (“what the body does to the drug,” or *pharmacokinetics*). Others influence the therapeutic effects or risk of *adverse drug events* (ADEs) (“what the drug does to the body,” or *pharmacodynamics*). *Precision*

medicine incorporates pharmacogenetic, clinical, environmental, and lifestyle factors into prescribing decisions.

Individual differences in drug metabolism can be partially attributed to *variants* (alterations of the DNA sequence) in genes that code for *metabolizing enzymes* responsible for drug breakdown. *Cytochrome P450* (CYP450) is a superfamily of enzymes expressed in the liver, intestinal tissue, and elsewhere that are involved in drug metabolism. *Alleles* (versions of the same gene with one or more variants) of genes coding for CYP450 and other metabolizing enzymes are identified using the “star (*) nomenclature,” where *1 is the reference sequence to which all alleles are compared and generally the functional enzyme.⁶ The activity of each allele is assessed and determined based on in vitro activity and in vivo evidence for associated drugs (*gene–drug pair/interaction*)⁴ (Table 2). The functional *phenotype* or *metabolizer status* resulting from the combined effect of both alleles is categorized using standard nomenclature: *poor*, *intermediate*, *normal*, *rapid*, and *ultrarapid*. This results in a spectrum of possible enzyme activity ranging from no function in poor metabolizers to increased function in ultrarapid metabolizers. Medications may be administered as inactive prodrugs or active drugs. Prodrugs are activated by the process of metabolism as they are transformed into active molecules. In contrast, active

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Table 1. Definitions of key terms and resources in the field of pharmacogenetics.

Pharmacogenetics	Study of individual or a few genes and their effect on the variability of drug responses
Pharmacogenomics	Field that combines pharmacology and genomics to study how all genes in the genome affect the drug response
Pharmacokinetics	What the body does to the drug, including absorption, distribution, metabolism, and elimination
Adverse drug event (ADE)	Harm caused by the use of a drug
Pharmacodynamics	What the drug does to the body, including therapeutic response and adverse effects
Precision medicine	The provision of treatments and preventions based on an individual's genetic, environmental, and lifestyle factors
Alleles/gene variants	Forms of the same gene with small differences in the DNA sequence/alterations of the most common DNA sequence of a gene
Metabolizing enzymes	Enzymes that are responsible for the breakdown of molecules and chemicals, including drugs, to metabolites. During the process of metabolism, drugs can be activated (prodrug → active drug) or fully or partially inactivated (active drug → partially active or inactive metabolites)
Cytochrome P450 genes and enzymes	Enzymes encoded by the cytochrome P450 genes and expressed primarily in the liver are involved in the synthesis and metabolism of various molecules and chemicals, including drugs. Each cytochrome gene is named with CYP, followed by the gene's subgroup and a number of the gene within the subgroup (e.g., <i>CYP2D6</i>)
Star (*) alleles	Combinations of genetic variants (haplotypes) in drug metabolism genes are designated using "star nomenclature." Star alleles are reported to cause no, decreased, normal, or increased function of the enzyme
Gene–drug pair/interaction	Change in the effect of a drug due to differences in a gene
Metabolizer phenotypes	Description of clinical phenotypes based on the combined impact of both alleles Normal metabolizer: fully functional metabolizing enzyme activity Rapid metabolizer: increased enzyme activity compared to normal metabolizers, but less than ultrarapid metabolizers Ultrarapid metabolizers: increased enzyme activity compared to rapid metabolizers Intermediate metabolizer: decreased enzyme activity compared to normal metabolizer, but more than poor metabolizers Poor metabolizer: little to no enzyme activity
Drug–drug interaction (DDI)	Change in the effect of a drug due to the presence of another drug in the body
Pharmacogene Variation Consortium (PharmVar)	Repository for pharmacogene allelic variation to facilitate the interpretation of pharmacogenetic test results for precision medicine
Pharmacogenomics Knowledge Base (PharmGKB)	Resource sponsored by the National Institutes of Health that curates information on human genetic variation and drug responses
Clinical Pharmacogenetics Implementation Consortium (CPIC)	International group interested in facilitating the clinical use of pharmacogenetics testing through the creation of peer-reviewed and evidence-based gene/drug clinical practice guidelines

drugs can be inactivated by metabolism by being broken down into partially active or inactive metabolites (Fig. 1a). Knowing whether a prescribed medication is activated or inactivated by metabolism influences the clinical effects of altered enzyme function, and the risk of ADEs or drug–drug interactions (Fig. 1b).

Pharmacogenetic knowledge is rapidly changing with new evidence being produced at exponential rates due to active research. *PharmVar*, the *Pharmacogene Variation Consortium*, and *PharmGKB* resources, supported by the National Institutes of Health, curate and centralize pharmacogenetic information to facilitate the interpretation of pharmacogenetic testing.^{2,7} The Clinical Pharmacogenetic Implementation Consortium (CPIC) produces evidence-based clinical guidelines on gene–drug pairs and interactions,⁵ including statements regarding how recommendations apply to pediatric patients. Finally, the Food and Drug Administration (FDA) has provided lists of pharmacogenetic associations for which data support management recommendations and how drug labels have incorporated the data.^{8,9}

EXAMPLES OF PHARMACOGENOMIC RESEARCH SUPPORTING CLINICAL IMPLEMENTATION

Codeine and morphine

One of the most well-known gene–drug interactions in children associated with life-threatening ADEs and drug label changes is

CYP2D6 and codeine. While the prodrug codeine has minimal analgesic effects, its most active metabolite, morphine, has a 200-fold greater affinity for opioid receptors, provides potent analgesic effects, and has the potential to cause somnolence, respiratory depression, and death.¹⁰ Low production of morphine from codeine may result in inadequate pain control.

Codeine is metabolized to morphine by *CYP2D6*, the enzyme encoded by the *CYP2D6* gene. In vitro studies demonstrated variable morphine production by human liver tissue and purified enzymes based on *CYP2D6* genotypes.^{11–15} Liver enzymes isolated from ultrarapid metabolizers have higher morphine production when compared to enzymes from normal metabolizers, while enzymes from poor metabolizers produce little morphine. In vivo, poor metabolizers (prevalence of 0.4–5.4%¹⁶) have lower morphine production, less analgesia, and fewer ADEs compared to normal and ultrarapid metabolizers.^{17–27} These findings have been confirmed in children.²⁸

Given the low potency, codeine was considered safe for outpatient use, but reports of severe ADEs in infants of breastfeeding mothers who were taking codeine raised concern. High morphine concentrations were found in symptomatic infants of breastfeeding mothers taking codeine.^{29,30} In most cases, the high morphine concentration was due to the dose of codeine, although some were also identified as *CYP2D6* ultrarapid metabolizers. The FDA advised caution when prescribing codeine

Table 2. Example drug–gene pairs for medications prescribed to children with significant evidence for recommendations in prescribing actions as defined by the Clinical Pharmacogenetics Implementation Consortium.

Drug	Gene
Allopurinol	<i>HLA-B</i>
Aminoglycoside antibacterials	<i>MT-RNR1</i>
Amitriptyline	<i>CYP2C19</i> <i>CYP2D6</i>
Atomoxetine	<i>CYP2D6</i>
Azathioprine	<i>TPMT</i> <i>NUDT15</i>
Carbamazepine	<i>HLA-A</i> <i>HLA-B</i>
Citalopram	<i>CYP2C19</i>
Clopidogrel	<i>CYP2C19</i>
Codeine	<i>CYP2D6</i>
Escitalopram	<i>CYP2C19</i>
Fluvoxamine	<i>CYP2D6</i>
Ibuprofen	<i>CYP2C9</i>
Lansoprazole	<i>CYP2C19</i>
Mercaptopurine	<i>TPMT</i> <i>NUDT15</i>
Nortriptyline	<i>CYP2D6</i>
Omeprazole	<i>CYP2C19</i>
Ondansetron	<i>CYP2D6</i>
Pantoprazole	<i>CYP2C19</i>
Paroxetine	<i>CYP2D6</i>
Phenytoin	<i>HLA-B</i> <i>CYP2C9</i>
Sertraline	<i>CYP2C19</i>
Simvastatin	<i>SLCO1B1</i>
Succinylcholine	<i>RYR1</i> <i>CACNA1S</i>
Tacrolimus	<i>CYP3A5</i>
Tramadol	<i>CYP2D6</i>
Voriconazole	<i>CYP2C19</i>
Warfarin	<i>CYP2C9</i> <i>CYP4F2</i> <i>VKORC1</i>

to a breastfeeding mother who is an ultrarapid metabolizer.³¹ The prevalence of ultrarapid metabolizer status varies depending on the biogeographic population,³² but can be >10% in certain groups including Oceanian, Ashkenazi Jewish, and Middle Eastern populations.¹⁶

In 2009, a 2-year-old child with sleep apnea was reported to have died after taking codeine following an uncomplicated adenotonsillectomy.³³ Postmortem analysis revealed high morphine levels and functional duplication of *CYP2D6* leading to ultrarapid metabolizer phenotype. After review of ADEs reported in children taking codeine after tonsillectomy and/or adenoidectomy (T&A) and who had altered *CYP2D6* metabolism,^{34,35} the FDA issued a new boxed warning stating codeine was contraindicated in children following a T&A.³⁶ In 2014, CPIC guidelines strongly recommended avoidance of codeine in ultrarapid metabolizers due to potential for toxicity and in poor metabolizers due to the lack of efficacy.^{36,37} While codeine prescriptions for children have

decreased since the initial FDA warning in 2013, use has persisted in some pediatric practices.^{38,39}

After reviewing ADEs reported over a 45-year period in children under the age of 18 years, the FDA identified >60 cases of severe breathing problems and 24 deaths following codeine administration.⁴⁰ In 2017, the FDA updated codeine drug labels to strengthen their warnings, including a contraindication for codeine to treat pain or cough in children under 12 years of age. A new warning was also added, recommending against codeine use in adolescents aged 12–18 years who have underlying breathing issues, such as obstructive sleep apnea, and in breastfeeding mothers.

Some have advocated for an exception to the FDA contraindication if pharmacogenetic testing is done, which could enable safe codeine use.⁴¹ By eliminating codeine as an option to treat pain, clinicians have resorted to alternative analgesics, including more potent opioids, with a higher risk of serious ADEs and which also have gene–drug interactions. Patients with sickle cell disease often require opioids when they are in crisis, and codeine was frequently used as it is the only Schedule III opioid analgesic available in the United States. Incorporation of *CYP2D6* testing into clinical practice with a clinical decision support tool within the electronic health record (EHR) has been demonstrated to be a safe and effective way to prescribe codeine to children with sickle cell disease while preventing codeine use after T&A and in patients with *CYP2D6* ultrarapid and poor metabolizer genotypes.⁴² Further research is required to identify other patient populations and indications in which the benefits of pharmacogenetic-guided codeine use outweigh the risks.

With the removal of codeine from many pediatric formularies, tramadol may be used more frequently for pain management. However, tramadol is also a substrate of *CYP2D6* metabolism and requires transformation into an active metabolite to provide pain relief.⁴³ Similar to codeine, poor metabolizers are at risk of inadequate pain control and ultrarapid metabolizers have a higher risk of ADEs.⁴⁴

Thiopurines

Azathioprine (a prodrug of mercaptopurine), mercaptopurine, and thioguanine are thiopurine immunosuppressants prescribed for pediatric dermatologic, gastrointestinal, oncologic, and rheumatologic diseases. Their ADEs include myelosuppression, pancreatitis, and hepatotoxicity, and their use may carry an increased risk of lymphoma.⁴⁵ All three drugs are considered prodrugs and metabolized to active thioguanine nucleotides (TGNs). Thiopurines have significant interactions with two pharmacogenes, thiopurine methyltransferase (*TPMT*) and nudix (nucleoside diphosphate-linked moiety X)-type motif 15 (*NUDT15*). Each of these genes strongly influences the clinical response and development of ADEs.⁴⁶ Preemptive (pre-prescription) genetic testing for one or both of these genes has become routine for some pediatric subspecialists.

The interactions between *TPMT* and mercaptopurine, to which azathioprine is converted, are complex.^{46,47} *TPMT* inactivates mercaptopurine through methylation, converting the drug to methylmercaptopurine base and thus decreasing the amount of parent drug available to produce active TGNs. However, *TPMT* also acts on a secondary metabolite of mercaptopurine, thioinosine monophosphate (TIMP), and converts it to methyl-TIMP, which has immunosuppressive effects and contributes to hepatotoxicity. In vitro studies have shown that mercaptopurine's conversion to methylmercaptopurine was lower in cells and organ tissues isolated from intermediate metabolizers and absent in poor metabolizers, when compared to normal metabolizers.^{48–51} In poor metabolizers, proteasomal degradation of *TPMT* was responsible for enzyme deficiency.^{52–54}

Clinically, *TPMT* poor metabolizers are at high risk for severe life-threatening myelosuppression due to toxic TGN levels.^{47,55} While

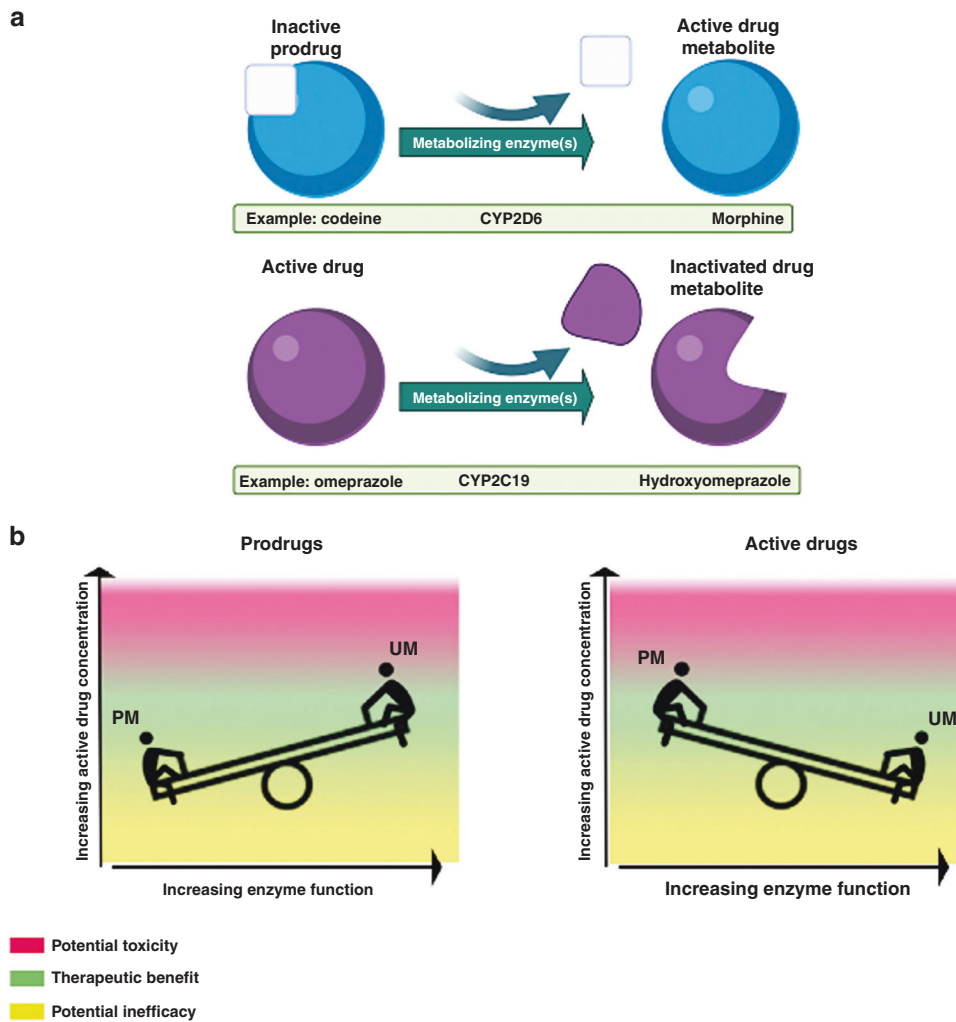


Fig. 1 The relationship between prodrugs, active drugs, inactivated drug metabolites, and metabolizer status. **a** Inactive prodrugs (top) need to be metabolized into an active drug metabolite to have therapeutic effect. In contrast, when an active drug is administered, metabolism of the drug can result in an inactivated drug metabolite. **b** Since prodrugs (left) are metabolized to an active form of the drug to achieve therapeutic effect, poor metabolizers that have low enzyme function will have low active drug concentrations and are at risk for inefficacy. Ultrarapid metabolizers that have high enzyme function are at risk of high active drug concentrations and potential toxicity. Active drugs (right) are metabolized into inactive drugs that have minimal or no therapeutic effect. Poor metabolizers are therefore at risk of high concentrations of active drugs and thus potential toxicity, while ultrarapid metabolizers will have low concentrations of active drug and may not achieve therapeutic efficacy.

intermediate metabolizers have higher TGNs than normal metabolizers, many are able to tolerate full doses of mercaptopurine or azathioprine because of reduced methyl-TIMP levels.⁴⁶ Individualized mercaptopurine and azathioprine dosing based on TPMT phenotype and measurement of thiopurine metabolites can successfully treat acute lymphoblastic leukemia⁵⁶ and inflammatory bowel disease,^{57–59} while reducing ADEs.

TPMT testing identifies only a portion of patients at risk of myelosuppression. More recently, *NUDT15* variants have been demonstrated to affect thiopurine tolerability, especially in Asian and Hispanic patients. Thiopurines are metabolized into cytotoxic thioguanine triphosphate (TGTP), the primary antileukemic metabolite and significant contributor to myelosuppression.⁴⁶ *NUDT15* converts TGTP to thioguanine monophosphate, a less toxic metabolite. In vitro, *NUDT15* decreases thiopurine cytotoxicity by inactivating thiopurine metabolites.⁶⁰ In children, *NUDT15*-deficient alleles led to increased levels of active thiopurine metabolites and cytotoxicity, requiring lower mercaptopurine doses.^{60–63}

CPIC updated guidelines in 2018 on thiopurine dosing based on *TPMT* and/or *NUDT15* genotypes.⁴⁶ Recommendations on initial

doses depend on the indication and the phenotype for each enzyme. While genotyping errors can occur and phenotypes can vary within metabolizer status (e.g., *TPMT* intermediate metabolizers), evaluation of markers of disease progression, myelosuppression or other toxicities, and even metabolites, will allow clinicians to adjust thiopurine doses from the genotype-guided starting doses.

PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are commonly prescribed to children.^{64–66} FDA-approved indications (with variable age ranges) include short-term therapy for gastroesophageal reflux disease, erosive esophagitis, peptic ulcer disease, and *Helicobacter pylori* eradication.^{67–69} PPIs are often used off-label in younger children, and for indications including eosinophilic esophagitis (for which PPIs are considered standard of care) and some upper respiratory tract inflammatory conditions, with conflicting data to support efficacy.^{70–72} These drugs act at the gastric cells by inactivating the proton acid pump, which suppresses acid secretion.⁷³ Common

ADEs of PPIs include headache and gastrointestinal distress, and children are more prone to respiratory infections.⁶⁷ Prior studies have suggested that the main route of metabolism is via sulfoxidation and hydroxylation through CYP450 enzymes with a correlation of intrinsic clearance of PPIs to enzyme function.⁷⁴ Omeprazole is considered a CYP2C19 clinical index inhibitor and has been used in drug–drug interaction studies.⁷⁵ All first-generation PPIs (omeprazole, lansoprazole, and pantoprazole) and the second-generation PPI dexlansoprazole are primarily metabolized by CYP2C19, with CYP3A4 playing a minor role.⁷³ Metabolism of the second-generation PPIs esomeprazole and rabeprazole are less CYP2C19-dependent.⁷³

Multiple adult studies have suggested that individuals with reduced CYP2C19 metabolism have increased exposure to first-generation PPIs compared to normal metabolizers.⁷⁶ In adults, poor metabolizers have been shown to have a greater response and less acidic gastric pH compared to intermediate and normal metabolizers.⁷⁷ Taken together, these studies suggest that CYP2C19 plays a clinically relevant role in PPI efficacy. CPIC guidelines are available to guide use of CYP2C19 metabolizer status for PPI selection and dose.⁷⁸

Prior studies have suggested increased CYP2C19 function in children compared to adults, thus the association of CYP2C19 function and clinical outcomes of PPI use should be carefully considered in the pediatric population.⁷⁹ For pediatric patients, pantoprazole and lansoprazole are the two most commonly investigated PPIs with respect to CYP2C19 effects. These studies have shown that poor metabolizers have higher exposure compared to normal metabolizers with delayed clearance and longer drug half-life.^{80,81} Clinical studies of children taking lansoprazole have associated ADEs and efficacy with CYP2C19 metabolizer status.⁸² The data for omeprazole are less clear and include some studies that show no association of outcomes with CYP2C19 genotype.^{83,84} However, a recent study showed reduced PPI efficacy in CYP2C19 ultrarapid metabolizers vs. those with reduced or normal CYP2C19 function.⁸⁵ Data for infants are lacking and would be of interest given the very low CYP2C19 function observed in fetal and neonatal periods, followed by PPI clearance approximating adult values ~6 months of age.^{86,87} In a cohort of children under 3 years of age (median age 7 months), increased upper respiratory infections were observed in normal metabolizers compared to those with increased CYP2C19 function.⁸⁸ Taken together, these data suggest that CYP2C19 genotype can predict PPI plasma concentrations, efficacy, and toxicity in children, and support the use of CYP2C19 data to guide PPI dosing, particularly after the neonatal period.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) increase serotonergic activity by decreasing presynaptic serotonin reuptake.⁸⁹ SSRIs are the most common antidepressant class used in pediatric patients.⁹⁰ Some SSRIs are FDA approved for some pediatric indications such as depression and obsessive compulsive disorder, but are commonly prescribed off-label in pediatric and adolescent patients for indications that have adult FDA approval such as anxiety disorders, post-traumatic stress disorder, and premenstrual dysphoric disorder.⁹¹ Common pediatric SSRI ADEs include activation, gastrointestinal upset, and sleep disturbance.⁹²

Some SSRIs, including sertraline, citalopram, and escitalopram, are extensively metabolized by CYP2C19, with other CYP450 enzymes contributing to a lesser extent.⁷⁹ Paroxetine and fluvoxamine are primarily metabolized by CYP2D6, while both CYP2D6 and CYP2C19 contribute significantly to fluoxetine metabolism.⁷⁹ In vitro studies correlate the effect of CYP variants and SSRI concentrations, and active drug and metabolite concentrations have been observed to correlate with the functional status of the CYP enzyme primarily responsible for

drug metabolism.⁷⁹ Poor and intermediate metabolizers have higher plasma concentrations than normal, rapid, or ultrarapid metabolizers.⁹³ There are CPIC guidelines pertaining to five of the most commonly used SSRIs to assist in using CYP2D6 metabolic status for dosing of paroxetine and fluvoxamine and CYP2C19 status for sertraline, escitalopram, and citalopram. These guidelines generally suggest reduced starting dose or alternative therapy in poor metabolizers to avoid ADEs and alternative therapies in ultrarapid metabolizers to avoid inefficacy.⁷⁹

For children and adolescents, the level of evidence for pharmacogenomic effects of CYPs varies across SSRIs. The data regarding the association of citalopram and escitalopram show mixed results. One small pediatric study did not show an association of citalopram and escitalopram concentrations or clinical symptoms to CYP2C19 genotype.⁹⁴ Another study suggested that ultrarapid metabolizers had slower escitalopram dose escalation over time compared to other metabolizers, although there was no association with the clinical endpoint point of irritability.^{94,95} In contrast, one pediatric study showed poor and intermediate CYP2C19 metabolizers have higher citalopram/escitalopram plasma levels, although clinical effects were not reported in this study.⁹⁶ Also, one study showed a higher rate of discontinuation of citalopram/escitalopram in poor metabolizers compared to faster metabolizers, likely related to increased ADEs.⁹⁷ There are three prior pediatric studies that do not suggest an association of CYP2C19 function and pediatric response or toxicity to sertraline,^{97–99} although another study found that children with reduced CYP2C19 metabolism had fewer ADEs than normal metabolizers, opposite of findings in adults.⁹² Fluoxetine, which is metabolized by CYP2D6 into an active metabolite, does not have CPIC guidelines. Pediatric studies investigating CYP2D6 metabolizer status and fluoxetine response did not show a difference in active metabolites or clinical outcomes.^{100,101} Thus, taken together the pediatric evidence for using CYP450 genetic testing for SSRI dosage guidance in youth is mixed and requires further study.

Some studies have examined associations of SSRI pharmacodynamic targets to attempt to improve pediatric efficacy. Two studies showed a correlation of the variants that encode the serotonin transporter and receptor, *SLC6A4* and *HTR2A*, on the dose and response of sertraline⁹⁸ and fluoxetine.¹⁰¹ Another study showed an association between the serotonin transporter *SLC6A4* and citalopram-related agitation.¹⁰² Although candidate genes are emerging to predict pediatric response to SSRIs, further work in this area is needed prior to clinical implementation.

ADHD MEDICATIONS

ADHD is a common pediatric disorder with evidenced-based guidelines suggesting medication as a first-line treatment for children older than 6 years of age.¹⁰³ Stimulants are most commonly used as first-line agents, but non-stimulants (atomoxetine, clonidine, and guanfacine) are commonly used as second-line treatments or for certain populations.¹⁰³ Most methylphenidate- and amphetamine-containing medications are FDA approved to treat ADHD in children 6 years and older, as are atomoxetine, clonidine, and guanfacine.¹⁰⁴ Despite these options, there is often heterogeneity in response to ADHD medications, which might be related to genetic factors.¹⁰⁵

Methylphenidate is not metabolized significantly by any CYP450 enzymes, while some amphetamine medications (e.g., dextroamphetamine) utilize CYP2D6 as a primary metabolic pathway.¹⁰⁶ There are no guidelines or adult data to suggest dosing of stimulants based on genotype. Overall, many reports propose multiple candidate genes for pediatric response to stimulants, although these often have inconsistent evidence.¹⁰⁵ Catechol-*o*-methyltransferase, an enzyme that inactivates dopamine and norepinephrine, the targets of methylphenidate, is the

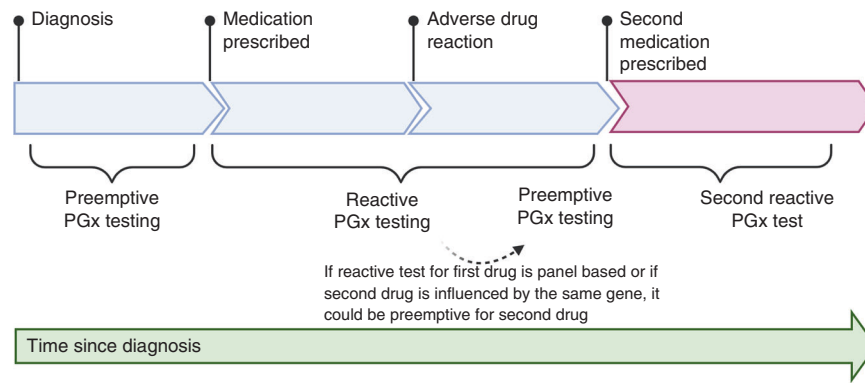


Fig. 2 A timeline of pharmacogenetic testing to demonstrate preemptive vs. reactive testing. Pharmacogenetic (PGx) testing is preemptive if it occurs prior to the prescription of a medication affected by the gene tested. If a panel of genes is tested or if a second medication influenced by the same gene is prescribed, a reactive test can be preemptive for the second medication, indicated by the dotted arrow. Clinical events are indicated by the pins along the timeline and brackets indicate when a test would be considered preemptive or reactive.

most extensively studied. Results indicate that gene variants resulted in decreased enzyme activity¹⁰⁷ and decreased medication response,^{108,109} although conflicting data are published.¹¹⁰ Thus, at this time there is insufficient evidence for using pharmacogenomics to guide stimulant dosing.

With regard to the non-stimulant medications used in ADHD treatment, atomoxetine, a selective norepinephrine reuptake inhibitor,^{110,111} is metabolized by CYP2D6 and to a lesser extent CYP2C19.¹¹² Pediatric studies suggest that CYP2D6 poor metabolizers had a better response to atomoxetine than normal metabolizers, yet the poor metabolizers also experienced increased ADEs.^{112,113} Atomoxetine has guidance for dosing based on CYP2D6 from the FDA label and CPIC. The FDA label for atomoxetine suggests CYP2D6 poor metabolizers should reach a maximum dose of 1.2 mg/kg/day, while others can go to a maximum dose of 1.4 mg/kg/day.¹¹⁴ CPIC guidelines recommend the appropriate timing to titrate atomoxetine dose based on CYP2D6 genotype and suggest that CYP2D6 ultrarapid metabolizers will likely not achieve appropriate efficacy from this drug at standard dosing regimens.¹¹² If a clinician is prescribing atomoxetine, CYP2D6 testing may aid in determining the titration schedule and target dose.

ONDANSETRON

Ondansetron is a 5-HT₃ antagonist commonly prescribed to reduce acute nausea and vomiting in pediatric patients. Metabolism of ondansetron is through several CYP enzymes: CYP3A4, CYP1A2, CYP2D6, and CYP1A1.¹¹⁵ Although it only accounts for ~30% of the metabolism of ondansetron,¹¹⁶ CYP2D6 variation can influence exposure and efficacy of the drug. Adult CYP2D6 ultrarapid metabolizers are more likely to continue to experience nausea and vomiting than normal metabolizers because of reduced exposure.^{117,118} One study in pediatric stem cell transplant patients confirmed the association between CYP2D6 ultrarapid metabolizers and increased episodes of emesis due to chemotherapy.¹¹⁹ The CPIC guideline for ondansetron suggests that an alternative antiemetic agent (e.g., granisetron) be used in CYP2D6 ultrarapid metabolizers.¹²⁰

Ondansetron efficacy also depends on pharmacodynamics. The drug prevents serotonin from binding to vagal afferent nerves after release from the intestinal enterochromaffin cells, which decreases vagus nerve signaling, reducing serotonin release in the brainstem.^{120,121} There are large interindividual differences in binding of ondansetron to the 5-HT₃ receptors, and efficacy partially correlates with receptor occupancy.^{122,123} Variants in *HTR3B* have been associated with early efficacy of ondansetron,^{124,125} but more research is needed, especially in pediatric patients.

CLINICAL PHARMACOGENETIC TESTING

There are several potential approaches to clinical pharmacogenetic testing. Depending on the drug, single-gene or panel-based tests are available. Clinicians must also decide on the timing of testing. “Reactive” testing is pursued at the time of prescribing the associated drug or after an ADE has been experienced^{126–128} (Fig. 2). The clinical utility of the results could be limited by the turnaround time for the test, particularly if a drug needs to be prescribed immediately. This obstacle could be overcome with point-of-care, rapid turnaround testing.¹²⁸ Alternatively, preemptive testing is performed in advance of prescribing decisions so that turnaround time is not an issue (Fig. 2). Results are available (e.g., in the EHR) for all prescribers. Given readily available technology to test multiple variants across multiple genes at low cost, many have advocated for a preemptive, panel-based pharmacogenetic testing strategy.^{126,127} Large studies have demonstrated that >90% of patients who undergo pharmacogenetic testing harbor at least one actionable variant, and, further, that most patients are exposed to at least one of the associated drugs.^{129,130} As costs for panel-based testing decrease, these data support a preemptive panel-based strategy.^{129,130} However, reimbursement by insurance companies has been identified as a barrier to implementation.^{131,132}

For pediatricians to use pharmacogenetic data in routine clinical practice, they must have access to a valid, relevant testing assay with clear, interpretable, actionable results with appropriate turnaround time.¹²⁶ Since most physicians have not received formal pharmacogenomics education and do not feel adequately informed about pharmacogenetics,^{133,134} pediatricians should be aware of resources that provide guidance in the interpretation of clinical pharmacogenetic tests, such as CPIC and PharmGKB. Several pharmacogenetics conferences offer continuing education credits, and for those interested in a more thorough understanding, there are certificate programs in pharmacogenetics for clinicians.

Ensuring that pharmacogenetic results are easily accessible in the EHR to all healthcare team members, including those outside the institution or the laboratory that performed the test, is an area of opportunity for implementation research. The EHR is the logical place to record results and create decision supports for current and future prescribers. Further, EHRs can be linked to pharmacogenomic records or biobanked specimens to provide research resources to further advance pharmacogenetics.^{135,136} Utilizing the EHR in this way requires collaboration of prescribers, pharmacists, laboratories, pharmacologists, and bioinformaticians.

Many institutions, healthcare systems, and countries are implementing pharmacogenomics via various strategies.¹³⁷ In the USA, some institutions are moving beyond recording pharmacogenomic data in the EHR by providing clinical decision

support; these alerts are activated when a drug is being ordered for which a patient has an actionable genotype.^{137,138} Thailand has implemented wallet-sized plastic cards to record pharmacogenomic results that patients carry and can present to medical providers.¹³⁹ Ubiquitous Pharmacogenomics is a European effort to preemptively obtain pharmacogenomic testing, embed these data in the clinical record, provide patients with wallet-sized cards with pharmacogenomic data, and utilize an electronic clinical decision support system to notify prescribers when a patient has a risk genotype.¹³⁷

PERSPECTIVE: RECOMMENDATIONS FOR PEDIATRICIANS

For pediatric researchers, the examples provided herein demonstrate the spectrum of the maturity of pharmacogenetic research for various drugs. The association of variable CYP2D6 function, predicted by *CYP2D6* genetic variants, to codeine activation to morphine was one of the sentinel discoveries in the field of pharmacogenetics. Further research exploring the clinical impact of this gene–drug interaction revealed potential toxicity from therapeutic doses of codeine affecting neonates, infants, and children. The accumulation of evidence led to regulatory and practice changes. On the other hand, for ondansetron, the evidence for the drug–gene interaction in adults is robust, but validation in pediatric cohorts is lacking. While some advocate for extrapolation of adult data to adolescents and children, there may be unique drug–gene interactions in younger patients. For SSRIs, one pediatric study indicated that ADEs are more common among CYP2C19 normal metabolizers than poor metabolizers, the opposite of what is reported in adults.⁹² While not discussed in our earlier examples due to infrequent prescription in pediatrics, for simvastatin, an increased effect size of *SLCO1B1* variation is seen in children and adolescents vs. adults.¹⁴⁰ These examples motivate validation of pharmacogenetic associations using data from pediatric populations prior to clinical implementation. Furthermore, the tremendous physiologic and metabolic changes that occur during childhood (and particularly in infancy and adolescence) provide the opportunity for the discovery of novel, pediatric-specific drug–gene interactions.

It is important to generate high-quality evidence to support clinical implementation of pharmacogenomics into pediatric practice, the hallmarks of which are: (1) adequate sample size. Many pediatric pharmacogenetic studies are of inadequate sample size to provide power to detect a difference between groups, leading to inappropriate reporting of negative findings (type II error). Collection of large cohorts of drug-exposed children representing the full spectrum of genetic variants can be difficult, particularly for drugs that are infrequently used in children. Large biobanks are one potential solution to gathering sufficient sample size. (2) Clinically meaningful endpoints. The progression of the codeine–*CYP2D6* association from research to regulatory action was facilitated by the documentation of severe, life-threatening events, and deaths attributed to the drug–gene interaction. Likewise, clinical implementation of *TPMT* and *NUDT15* testing to guide thiopurine dosing was supported by the observation of potentially life-threatening white blood cell suppression. While not all pharmacogenetic associations will be associated with such dramatic outcomes, studies must include clinically relevant outcomes (e.g., for ondansetron, nausea and vomiting impacting the quality of life, and length of hospital stay). For drugs with well-known therapeutic and toxic concentrations (e.g., voriconazole), pharmacokinetic studies may suffice, but for many others, pharmacodynamic data will be required. (3) Inclusion of participants representing those exposed to the drug with respect to age, indication, and ancestry. Drugs often have pediatric- and age-specific indications (e.g., nonsteroidal anti-inflammatory drugs for closure of patent ductus arteriosus), which may have specific pharmacogenetic associations. Neonates, infants, children, and

adolescents may have developmentally regulated expression of drug transporters, metabolic enzymes, and drug response targets, leading to age-specific associations. Many genetic and pharmacogenetic studies have focused on those of European ancestry. Since the spectrum and prevalence of genetic variants often vary across ancestral populations, it is imperative to study diverse cohorts to make the findings relevant to clinical care. (4) Robust assessment of the target gene. While full sequencing for each gene of interest may be cost prohibitive, researchers must ensure that the most important and frequent variants for the gene(s) of interest, which may vary depending on the population, are assessed.

Clinical implementation of pharmacogenetics in pediatrics is challenging^{132,134,136,137,141,142} and further discussion of clinical implementation is beyond the scope of this review. However, additional high-quality studies with these four hallmarks will propel the field of pediatric pharmacogenetics towards clinical implementation.

Pediatric clinicians can expect increasing evidence supporting the incorporation of pharmacogenetics into their care of children. However, care must be taken to critically evaluate the evidence. It has been common for some commercial pharmacogenetic testing companies to take a “more is better” approach to their recommendations, including genetic associations with very little or conflicting evidence into their pharmacogenetic test results.¹⁴³ Recent FDA actions have encouraged laboratories performing pharmacogenetic testing to provide only the results of the testing, without interpretation or guidance for the prescriber. While this may avoid the inappropriate reliance on poor quality studies to guide care, it also shifts the burden of interpretation to clinicians. It is important for pediatricians to have access to high-quality education about pharmacogenetics as more drug–gene interactions are demonstrated to have clinical validity for children.

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ADDITIONAL INFORMATION

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