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Clinically Relevant Pharmacogenomic Testing in Pediatric Practice

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Abstract

Clinicians and patients continue to convey interest in personalized medicine. The objective of personalized medicine is to improve healthcare by tailoring disease prevention, diagnosis, and treatment strategies for individuals based on their unique clinical history and genetic composition. This article offers an overview of pharmacogenomics, discusses caveats specific to pharmacogenomics in pediatric populations, provides evidence-based recommendations for pediatric clinicians, and offers insight regarding the future role of pharmacogenomics testing in pediatric medicine. Reviews of the current literature and thoughtful discussions are presented regarding the pharmacogenomics of antidepressants, codeine and oncologic, asthma, and immunomodulatory pharmacotherapies.

Keywords

pediatrics; pharmacogenomics; pharmacotherapy; genetics

Interest in personalized medicine and pharmacogenomics continues to rise as rapid advances in genomic technologies allow for the completion of ground-breaking endeavors such as the Human Genome Project, the HapMap Project, and the 1000 Genomes Project. Personalized medicine aims to improve health care by tailoring prevention, diagnosis, and treatment strategies to suit individual patients based on their unique clinical history and genetic composition. Pharmacogenomics, referring to the investigation of how genetics influence patient's response to pharmacotherapies, is a cornerstone of personalized medicine, and the number of clinical scenarios for which pharmacogenomics testing is relevant continues to increase. The era of truly individualized medicine, however, has not yet arrived: Evidence of improved clinical outcomes is limited, and pharmacogenomics testing for most drugs has neither been endorsed by expert committees nor is it being reimbursement by third parties (eg, insurance companies, health management organizations, and Medicaid). This is

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changing, however, as translational pharmacogenomics research progresses. This article offers an overview of pharmacogenomics, discusses the caveats specific to pediatric populations, provides evidence-based recommendations for pediatricians, and offers insight regarding the future role of pharmacogenomics testing in pediatric medicine.

What Is Pharmacogenomics?

Pharmacogenomics is the study of how genetic factors influence interindividual variability of drug response. Many clinicians may not be entirely familiar with its background and the terminology used in the pharmacogenomic literature. A brief review of the terminology is provided below and followed by a schematic (Figure 1) describing the various stages of translational research involved in the advancement of a pharmacogenomics test into clinical practice.

The coding sequence of DNA base pairs for a particular gene is the genotype, and a phenotype refers to a trait resulting from the protein product encoded by a gene. Examples of phenotypes include blood type, hair color, and the extent to which an individual metabolizes or responds to a certain pharmacotherapy. A gene's name is italicized and refers to its protein product (eg, the *CYP2D6* gene encodes for the CYP2D6 enzyme). The genotype is formed from 2 alleles per autosomal gene, 1 maternal and 1 paternal. Homozygotes possess 2 of the same alleles, and heterozygotes possess 2 different alleles. The most common allele in a population is referred to as the wild type, and allele frequencies often vary from one patient population to the next.

Most sequence variations are single nucleotide polymorphisms (SNPs, pronounced "snips"). A SNP is a single DNA base pair substitution that may result in a different gene product. A polymorphism that does not result in a changed protein product is often referred to as a silent mutation or a synonymous polymorphism. SNPs can be classified as structural RNA polymorphisms (srSNPs), regulatory polymorphisms (rSNPs), or polymorphisms in coding regions (cSNPs): srSNPs alter mRNA processing and translation, rSNPs alter transcription, and cSNPs alter protein sequence and function. SNPs by themselves may exert a pharmacokinetic effect (ie, how the body processes the drug), a pharmacodynamic effect (ie, how the drug affects the body), or both. Often they may act in concert with other genes or with other genetic factors (eg, promoter or enhancer regions).

Variations in response to pharmacotherapies can result from genetic polymorphisms affecting pharmacokinetics (eg, codeine concentrations in blood are related to *CYP2D6* phenotype status), pharmacologic targets (eg, VKORC1 is a genetically influenced target of warfarin), or other factors related to the drug's mechanism of action or the disease-related biologic pathways (eg, CETP is involved in cholesterol metabolism but affects response to statin therapy). Genome-wide association studies (GWAS) typically investigate the associations of predefined phenotypes and millions of SNPs measured in each of hundreds or thousands of patients. This approach has revealed countless candidate genes for further investigation, but most have not matured into practical clinical applications. More recently, phenome-wide association studies (PheWAS) have been reported.¹ They investigate the relationship between genetic variation and networks of phenotypes. The power of both

GWAS and PheWAS techniques can be increased by combining data from multiple patient cohorts; however, combining cohorts for a GWAS requires homogeneity regarding phenotype definitions in all cohorts. A PheWAS approach is advantageous because it allows dissimilar phenotype definitions among cohorts. The flexibility of this method should allow for expedited translation of pharmacogenomics research into clinical applications, but prospective randomized trials evaluating improvement in patient outcomes are likely to remain the gold standard for determining the clinical significance of a pharmacogenomics test. Figure 1 illustrates that transgenic studies and functional analysis are also critical in the process of determining the genotype–phenotype relationship and translating pharmacogenomics research into the clinical setting.

Caveats of Pediatric Pharmacogenomics

Ontogeny affects all levels of drug pharmacokinetics—absorption, distribution, metabolism, and excretion. Developmental changes also affect drug pharmacodynamics, influencing the expression of drug targets such as ion channels, transporters, receptors and downstream signal transduction pathways.

When considering pharmacogenomics in pediatric patients, developmental changes in the expression of phase I drug biotransformation enzymes (eg, the cytochrome P450 family of enzymes) and phase II conjugating enzymes (eg, sulfotransferases and uridine 5′-diphosphoglucuronosyltransferases) must be considered. The developmental expression of several of these metabolism pathways has different rates during childhood. Therefore, a genotype–phenotype relationship established in adults does not necessarily apply to children, and accounting for the changes in gene expression during development is paramount for understanding the genotype–phenotype relationships in pediatric populations. Although pharmacogenomic studies are not overly common in pediatrics, this is changing and the number of pediatric clinical scenarios for which pharmacogenomics testing is applicable is expanding. A discussion of the advantages and limitations of a few of these scenarios follows.

Oncologic and Immunomodulatory Pharmacotherapy

Mercaptopurine

An inhibitor of DNA synthesis, mercaptopurine (6-MP) preferentially targets highly proliferative cells (eg, malignant cells, myeloid cells, gastrointestinal cells) and has several oncologic and autoimmune indications. 6-MP has 3 separate metabolism pathways,² and the thiopurine methyltransferase (TPMT) pathway is the primary pathway. TPMT catalyzes the S-methylation of 6-MP leading to 6-MP metabolites.³ One in 500 patients is homozygous for a *TPMT* variant allele that codes for a nonfunctional TPMT enzyme, and 5% to 11% of patients are carriers (heterozygotes) of the variant *TPMT* allele. Reduced TPMT activity results in decreased metabolism of 6-MP,^{4,5} leaving patients at increased risk for developing 6-MP toxicities (eg, myelosuppression).² Genetic testing, therefore, is recommended by the Food and Drug Administration (FDA) prior to initiating 6-MP therapy, and clinicians should consider lower doses of 6-MP in their patients that are carriers of a variant *TPMT* allele and should consider treatments other than 6-MP for ALL patients that are homozygous for the

TPMT variant allele.⁵ Studies indicate that that dose reductions in deficient and intermediate metabolizers (homozygotes and heterozygotes, respectively, for the loss-of-function *TPMT* allele) of 6-MP are able to achieve optimal therapeutic effect while avoiding toxicity. Heterozygotes typically need a dose reduction between 35% and 50%, and homozygotes need a dose reduction of about 90%.^{3,4} Expression of *TPMT* does not change significantly during development,⁶ allowing use of these suggested dose reductions across the pediatric and adult spectrum. As azathiopurine is a prodrug of 6-MP, its pharmacokinetics involves *TPMT*, and prospective genotyping is recommended.⁷

Methotrexate

Methotrexate (MTX) is a folate antagonist that disrupts T cell activation and expression and also inhibits DNA and RNA synthesis. It has several oncologic and autoimmune indications, but patient response is highly variable⁶ and a significant lag phase occurs prior to onset of response.⁸ Several studies report a SNP at position 677 in the *methylene-tetrahydrofolate reductase (MTHFR)* gene is associated with reduced levels of *MTHFR* expression, higher incidence of toxicities, and increased risk for disease relapse ($n = 178$, $P = .003$).^{3,9–11} These associations, however, have not been consistently reported, and a 2012 meta-analysis including 24 studies investigating the 677 SNP and other *MTHFR* SNPs determined that evidence is insufficient to warrant any clinically useful recommendations regarding MTX dosing and genetic markers.¹¹ Differences and inconsistencies in the study findings likely resulted from small sample sizes and inhomogeneity among study groups regarding racial make-up, drug-dosing levels, and definitions of toxicity.

Tacrolimus

Tacrolimus, a calcineurin inhibitor used to prevent allograft rejection, is the most commonly used posttransplant immunosuppressant in the United States.⁷ Tacrolimus is metabolized primarily by CYP3A. Tacrolimus pharmacokinetics is highly variable among patients, and it has a narrow therapeutic index and significant toxicity risk.¹² Reported toxicities of tacrolimus include significant neuropsychiatric and renal problems and increased risk for development of lymphoma and other malignancies and susceptibility to infection. Nearly half of patients given a standard dose of tacrolimus are not within the therapeutic window when tested 2-weeks posttransplant ($P < .05$).¹³ Tacrolimus dosing requirements are significantly affected by CYP3A metabolism. The FDA black box warning recommends dose adjustments when tacrolimus is taken concurrently with other medications inhibiting or inducing CYP3A metabolism.¹² Genetic variants of CYP3A5 and CYP3A4 have recently been reported to significantly affect tacrolimus pharmacokinetics and dose requirements. CYP3A5*3, the most common nonfunctional variant allele of CYP3A5, and CYP3A4*22, a common reduced-function CYP3A4 allele are associated with increased levels of tacrolimus, resulting in increased risk of toxicity at standard doses.¹⁴ Evidence prompting the inclusion of CYP3A genotype for dosing recommendations of tacrolimus and other medications significantly metabolized by CYP3A continues to amass and may soon be incorporated into FDA labeling changes.

Asthma Pharmacotherapy

Asthma is one of the most common chronic diseases in children and adolescents. The 3 primary pharmacotherapies for asthma include beta-agonists, corticosteroids, and leukotriene modifiers. Medications in each of these classes can be associated with severe toxicity, and patient response is largely variable and dependent on individual's genetic make-up. Pharmacogenomic testing could, therefore be a useful tool for helping guide therapy and dosage-selection strategies for optimizing efficacy and avoiding toxicity.

Beta-Agonists

Beta-agonists for asthma therapy selectively (or exclusively) target the beta2 adrenergic receptor.¹⁵ Locus B16 of the gene encoding the beta2 receptor is a significant SNP locus; patients with arginine at this locus are more likely to respond and respond more quickly to beta-agonists than do those with glycine at the locus.^{3,16} About one sixth of Caucasians and one fifth of African Americans are homozygous for arginine at B16.¹⁵

Leukotriene Modifiers

Leukotriene modifiers are indicated as an alternative to low-dose inhaled corticosteroids in patients with mild asthma or as an adjunct to inhaled corticosteroids in patients with moderate or severe asthma. However, the literature suggests that nearly half of patients are nonresponders to leukotriene modifiers. Arachidonate 5-lipoxygenase is the first committed enzyme in the leukotriene biosynthetic pathway,¹⁵ and polymorphisms (SNPs and/or tandem repeats) in the encoding gene significantly affect patient's response to leukotriene modifiers. The SNPs lie mostly in the gene promoter region and result in decreased promotion of gene translation. Carriers therefore have reduced amounts of leukotrienes, and response to treatment with leukotriene modifiers (5-lipoxygenase inhibitors) is decreased (heterozygotes) or nonexistent (homozygotes for the variant allele).⁵ In the case of tandem repeats in the promoter region, carriers of at least one copy of the wildtype allele should have an improvement in their FEV₁ (forced expiratory volume in 1 second) during treatment while homozygous variant allele carriers are unlikely to see any improvement (n = 221, $P < .0001$).^{3,15} The prevalence of the homozygous SNP or minor allele number of copies is only about 3% in the US population.¹⁷ Despite a large effect size, no clear mandate for pharmacogenomics testing has been made because the prevalence of the polymorphisms is so low.

The gene encoding for the leukotriene C4 synthase protein also influences patient response to leukotriene modifiers. Children with wildtype alleles have more leukotriene C4 synthase activity than those with variant alleles (A at position 444 is wildtype, and C is the variant).³ Individuals with increased leukotriene C4 synthase activity have a stronger response to pharmacologic modification of the leukotriene pathway.⁵ Carrying even a single variant allele results in a decreased response to treatment with a leukotriene modifiers¹⁶; however, carriers of the variant allele are also at a decreased risk for asthma exacerbations (homozygous CC individuals have a 73% to 80% reduced risk for acute asthma exacerbations).³

Corticosteroids

Corticosteroids can be used to reduce airway inflammation, improve lung function, improve asthma symptoms, and reduce asthma exacerbations.¹⁵ However, nearly a third of children taking inhaled corticosteroids do not experience objective improvement of their asthma-related airway reactivity, and corticosteroids can be associated with serious adverse effects in children.¹⁶ The corticotrophin-releasing hormone receptor 1 (CRHR1) has been extensively studied for genetic polymorphisms that may influence response to corticosteroids. Many variants in CRHR1 have demonstrated associations with corticosteroid efficacy, but a robust biomarker is yet to emerge.

The *TBX21* gene, which encodes the transcription factor (t-bet), is responsible for the induction of Th1 cells, repression of Th2 cells, and associated with the pathophysiology of asthma.³ The H33Q SNP in *TBX21* is associated with higher responsiveness to corticosteroids in children,³ but only a small percentage of the population has that minor allele.¹⁸

A meta-analysis showed that across many cohorts of children, carrying a SNP in the FCER2 receptor gene (T2206C) is associated with lower FCER2 expression and increased hospital visits for pediatric asthma patients receiving inhaled corticosteroids (odds ratio 2.38). Furthermore, individuals with this polymorphism should be managed by a specialized pediatrician.¹⁸

Genetics influence susceptibility, severity, and response to treatment for pediatric patients with asthma. As larger, randomized, blinded clinical trials are completed in pediatric populations with asthma are completed, further pharmacogenomics guidance will be available to practitioners.

Antidepressants

Nearly 10% of primary care visits for patients aged between 6 and 17 years are psychiatry related.¹⁹ Selective serotonin reuptake inhibitors (SSRIs) are indicated for several depression related disorders; however, only 55% to 60% of pediatric patients benefit from SSRI therapy,²⁰ and an increased risk for suicidal behavior was associated and recognized by the FDA in 2004. Biomarkers to help guide pediatric treatments involving antidepressants and antipsychotics would be greatly beneficial, and much research effort has been devoted to this area. In the meantime, pediatricians should consider the robust research findings, although based on adult patient populations, regarding pharmacogenomics and suggested dose adjustments of the commonly prescribed antipsychotics and antidepressants (Table 1).

CYP2D6

Antidepressants are among the many drug classes that must be metabolized to their active form by CYP2D6 and are therefore referred to as “prodrugs.” *CYP2D6* has extensive genetic variability; more than 75 allelic variants have been identified in *CYP2D6*.²¹ Several variants result in reduced or no enzyme activity, and people who have more than two normally functioning alleles have exaggerated enzyme activity (gene amplification). Patients can be

classified as poor, intermediate, extensive, or ultra-rapid CYP2D6 metabolizers based on their genetic status alone²; the poor-metabolizer group including homozygotes for dysfunctional variants, and the ultra-rapid-metabolizer group having extra copies of functional alleles. Nearly 10% of Caucasians and 1% of Asians are poor metabolizers, and CYP2D6 metabolism appears to be concordant with genotype by 2 weeks of age.² Newer CYP2D6 classification systems (categories) involve both genetic status and concomitant medications interfering with CYP2D6 activity. Drugs such as amiodarone and fluoxetine inhibit CYP2D6 activity, while others (eg, rifampin, dexamethasone, and St John's wort) induce CYP2D6 activity. Clinicians should be aware that the efficacy of CYP2D6 prodrugs is greatly reduced by concomitant therapy with CYP2D6-inhibiting drugs (Table 2). For example, an extensive CYP2D6 metabolizer (based on genetic status) taking a CYP2D6-inhibiting concomitant medication should be considered a poor metabolizer and may require a higher dose. The classification systems considering concomitant medications are more accurate for correlating genotype with phenotype, but the older methods of classifications (based solely on genetic status) and naming are still widely used.²¹

Many antidepressants show significant differences in plasma drug levels with *CYP2D6* polymorphisms, including imipramine, doxipen, maprotiline, trimipramine, desipramine, nortriptyline, clomipramine, paroxetine, venlafaxine, amitriptyline, mianserin, trazadone, bupropion, nefazodone, citalopram, and sertraline.²¹ Suggested dose adjustments based on CYP2D6 metabolizer status are provided in Table 1.

Serotonin Transporter

The serotonin transporter is the main target for SSRIs,¹⁹ and the 5-HT *TLPR* is the most extensively studied region of the serotonin transporter gene. Adult carriers of the L allele respond better to SSRIs than noncarriers.²⁰ This has proven to be the case for most studies in children as well. In a study of Ashkenazi Jewish children, those with SS genotypes (non-L-allele carriers) had a lesser response to citalopram as evidenced by higher ratings on the Children's Depression Rating Scale and higher rates of suicidality than LS or LL allele carriers ($n = 74$, $P = .04$).²⁰ Similarly, in a study of pediatric Caucasian children with autism, children carrying an L-allele at the 5-HT *TLPR* locus responded more favorably (greater improvements in irritability scores and less insomnia and hyperactivity) to SSRIs ($n = 58$, $P < .001$).²²

GNbeta3

Another gene locus associated with response to SSRIs is *GNbeta3*. In general, children respond better to SSRIs than they do to older tricyclic antidepressants, but efficacy is not significantly different between the 2 drug classes in adult patient populations. However, in a case-control study of 169 Europeans with depression, young patients with the T allele responded to fluoxetine (an SSRI) and nortriptyline (a tricyclic antidepressant) equally ($n = 169$, $P < .001$).²³ About 50% of Europeans lack the T-allele, while only 20% of African Americans do not have the T-allele, suggesting that only 20% of young African American patients will respond well to treatment with tricyclic antidepressants.²³

Codeine and Breastfeeding Mothers

Response to codeine also depends on the *CYP2D6* gene; codeine must be activated to its more potent opioid metabolites (eg, morphine). Poor *CYP2D6* metabolizers require greater doses of codeine or may not benefit from codeine therapy. The pharmacogenomics of codeine has become a hot topic, especially regarding breastfeeding mothers. The debate was ignited with the publication in 2006 of a case report of an infant's death, apparently the result of metabolic polymorphisms. The evolution of this debate and the outcome of the case may be noteworthy to clinicians, as they illustrate the gravity of public and patient interest in pharmacogenomics testing. In this case, the breastfeeding mother had taken codeine regularly for about 14 days when her 13-day-old infant died from toxic levels of morphine. Unknown to her and the prescriber, both the mother and the infant were ultra-rapid *CYP2D6* metabolizers, resulting in a more rapid and extensive conversion of codeine to morphine. Although their ultra-rapid metabolism was not the only significant contributor to the infant's toxic response, a logical strategy for preventing similar deaths would be routine *CYP2D6* genotyping when prescribing codeine to breastfeeding mothers. However, after several investigations of this case examined the metabolic and excretion pathways of codeine in their entirety, the FDA did not recommend routine *CYP2D6* testing when prescribing codeine to breastfeeding mothers because several other factors, including rare genetic variations of other enzymes, proved necessary for reaching the opioid toxicity leading to the infant's death.

Future Perspectives

The examples discussed in this article provide some insight about how pharmacogenomic testing is maturing and slowly being integrated into the pediatric practice. They also illustrate the complexity of the multiple stages of research that pharmacogenomic applications must go through in order to be adopted as standard practice. In the future, pharmacogenomic data will continue to accumulate, and the clinical utility of many other pharmacogenomic tests may be uncovered. The FDA provides information on emerging pharmacogenomic tests and drug labeling on its Web site (www.fda.gov). Following its current trend, the FDA will require prospective randomized trials showing improvement in patient outcomes to determine the clinical significance of a pharmacogenomic test. Furthermore, cost-benefit analyses are likely to continue dictating policy regarding pharmacogenomic testing, and cost-benefit profiles should improve as technology advances and as information gathered from a single test becomes applicable to multiple medications and clinical scenarios. In the meantime, physicians should become familiar with the terms used in medical genetics and pharmacogenomics and begin to understand genetic contributions to the outcomes of drug therapy. For example, understanding the consequences of metabolizer status and the frequency of variants in a given population can be tremendously helpful when advising our patients about anticipating potential problems when taking specific medications and about making informed decisions about pharmacogenomic testing. This exchange of information alone may go a long way in improving therapy outcomes even when prospective pharmacogenomic testing is not routinely performed. Furthermore, an increasing number of patients will already have genotyping information

available when they come to us, and clinicians need to be aware of the many pharmacogenomic applications recommended by the FDA when genetic status is known.

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Figure 1.
Translating pharmacogenomics research into clinical practice.

Table 1Suggested Dose Adjustments.^a

<i>CYP2D6</i> Genotype	Imipramine	Doxepin	Trimipramine	Despramine	Nortriptyline	Clomipramine	Paroxetine
PM	30	35	35	42	53	60	65
IM	80	80	90	83	96	90	85
EM	130	130	130	125	119	110	115
UM	180	175	180	167	152	145	135

	Venlafaxine	Amitriptyline	Bupropion	Perphenazine	Haloperidol	Olanzapine	Risperidone
PM	70	75	90	30	75	60	85
IM	80	90	95	80	95	105	90
EM	105	105	105	125	100	120	100
UM	130	130	110	175	115	150	110

Abbreviations: PM, poor metabolizers; IM, intermediate metabolizers; EM, extensive metabolizers; UM, ultra-rapid metabolizers.

^a Percentages of standard dose have been approximated to the nearest 5%. Adapted from graphical information in Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry*. 2004;9:442–473.

Table 2

Medications that Inhibit CYP2D6.

Bupropion	Terbinafine	Clemastine	Halofantrine	Moclobemide
Cinacalcet	Amiodarone	Clomipramine	Hydroxyzine	Perphenazine
Fluoxetine	Cimetidine	Cocaine	Levomepromazine	Ranitidine
Paroxetine	Celecoxib	Diphenhydramine	Methadone	Reduced-haloperidol
Quinidine	Chlorpheniramine	Doxepin	Metoclopramide	Ritonavir
Duloxetine	Chlorpromazine	Doxorubicin	mibefradil	Ticlopidine
Sertraline	Citalopram	Escitalopram	Midodrine	Tripelennamine