Pharmacogenetic testing in children: What to test and how to use it

The use of pharmacogenetic testing to help drive decisions for medication management of patients with psychiatric illnesses is growing. It’s becoming increasingly common for patients or the parents of pediatric patients to request pharmacogenetic testing or to bring the results of prior testing to their appointment. In these situations, patients may ask clinicians to consider the recommendations from these testing reports, which rarely provide guidance specific to pediatric patients. However, this can be difficult for clinicians who did not receive education in pharmacogenetics and may not be familiar with the evidence or options for pharmacogenetic testing. Many of the pharmacogenetic associations identified thus far have been discovered in adults, but studies in pediatric patients are relatively rare. This article reviews pharmacogenetic testing and the evidence supporting it, and describes implementation of routine pharmacogenetics testing at a children’s hospital.

CASE
Testing leads to dose adjustment, improvement
Ms. R, age 16, presents with treatment-resistant major depressive disorder that is characterized by a significant neurovegetative burden and prominent anhedonia, as well as intermittent suicidal ideation without intent or plan. She reportedly did not improve after multiple medication trials, including citalopram (maximum dose 30 mg/d, treatment duration 8 weeks, good compliance), sertraline (maximum dose 150 mg/d, treatment duration 10 weeks, good compliance), fluoxetine (maximum compliance, but she failed to show improvement. Therefore, her provider decided to perform pharmacogenetic testing on her ANNOTATIONS/ANTONIO GUILLEM/PAULISTA/SHUTTERSTOCK

Disclosure
The author reports no financial relationships with any company whose products are mentioned in this article, or with manufacturers of competing products.
enzymes to the pharmacokinetics of neuro-psychiatric medications have been well-described; however, there is less evidence on whether variants in these genes are associated with treatment efficacy, especially in pediatric patients.\textsuperscript{8,9} CYP2D6 enzyme activity reaches adult levels soon after birth, but children may have higher CYP2C19 activity than adults.\textsuperscript{4} CYP3A4 also contributes to the metabolism of many medications; however, there is only weak evidence that genetic variants in CYP3A4 contribute to variability in the pharmacokinetics of these medications, and there are currently no dosing guidelines based on pharmacogenetics available for this gene.\textsuperscript{10}

As is common in the pharmacogenetic field, genotypes are denoted with a “star allele” (eg, *2) rather than positional nomenclature (eg, c.681G>A). The normal allele is usually designated as *1, and this result is given in the absence of the tested alleles. There is no consensus on the minimum set of alleles to be tested for most genes,\textsuperscript{11} so commercially available tests vary widely in what alleles are tested (and therefore what they exclude before calling a normal allele).\textsuperscript{12} The metabolizer phenotype for a patient is determined by taking into account the activity of each of the patient’s 2 alleles (eg, *1/*2). A patient is categorized as a poor-, intermediate-, normal- (extensive-), or ultra-rapid metabolizer. Generally, the allele definitions are widely agreed upon (what genetic variant or variants comprise the *2 allele) due to nomenclature committees for each gene; however, because there are no standards for interpretation, the interpretation of the activity of the alleles and conversion to metabolizer phenotype varies among clinics.\textsuperscript{13}

**Guidelines help with genotype-guided dosing**

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines describing the allele definitions, allele activity, and phenotypic interpretation.\textsuperscript{14} Evidence-based guidelines for genotype-guided dosing of selective serotonin reuptake inhibitors (SSRIs)\textsuperscript{4} and tricyclic antidepressants\textsuperscript{5,15} are available from CPIC. There is less guidance for antipsychotics,
although the Dutch Pharmacogenetics Working Group (DPWG) provides some guidance for aripiprazole and haloperidol.\textsuperscript{16}

Each CPIC guideline specifically addresses use in pediatric patients, indicating that there are relatively few studies in pediatrics, but “it may be appropriate to extrapolate these recommendations to adolescents or possibly younger children with close monitoring.”\textsuperscript{4} The DPWG guidelines do not mention whether or not the recommendations are applicable to children. Neither CPIC nor the DPWG provides guidance on when to test; however, the French National Network of Pharmacogenetics (Réseau national de pharmacogénétique) recommends CYP2D6 and CYP2C19 genotyping before initiating antidepressant treatment, especially in patients with a high risk of toxicity.\textsuperscript{16}

In the case above, Ms. R was determined to be a CYP2D6 ultra-rapid metabolizer. Because she showed some initial response to aripiprazole and venlafaxine ER, which are both metabolized by CYP2D6, these medications were very quickly titrated up, and the increased dosages produced the desired response. Venlafaxine is metabolized to the active metabolite O-desmethylvenlafaxine by CYP2D6. The DPWG recommends increasing the dose of venlafaxine in
CYP2D6 ultra-rapid metabolizers to 150% of the normal dose based on the decreased serum concentrations of venlafaxine and O-desmethylvenlafaxine in these patients. Aripiprazole is also metabolized by CYP2D6; however, the FDA and DPWG give no recommendations for ultra-rapid metabolizers, but do recommend reducing the dose of aripiprazole in CYP2D6 poor metabolizers.

Multiple studies in adults have analyzed the association between pharmacokinetic (CYP2D6 and CYP2C19) or pharmacodynamic genes (SLC6A4, HTR2A, and GRIK4) and outcomes, including some large clinical trials that conducted genome-wide association studies and meta-analyses across multiple studies. Most pharmacogenetic studies in psychotic patients are small, and very few have included pediatric patients. However, with more interest in neuropsychiatric pharmacogenetics, these studies are becoming more common.

**Limited evidence from studies of commercially available tests**

Several pharmacogenetic tests are commercially available, including some that focus on providing information that can be used specifically when prescribing psychiatric medications, such as the GeneSight Psychotropic test, CNSdose, Genomind, and Neuropharmagen.

In an industry-sponsored, nonrandomized clinical trial that included patients for whom prescribing decisions were made based on the GeneSight test, outcomes in adults were improved compared with treatment as usual, and inpatient stays were shorter, and pharmacy costs were reduced. In one of these studies, the authors noted that the traditional, single-gene analysis was not associated with improved outcomes, whereas the multiple gene combination (pharmacokinetic and pharmacodynamic genes) was associated with improved outcomes among patients with depression. However, when GeneSight was compared with treatment as usual in a small randomized trial, there was not a significant association between use of the test and improved outcomes among patients with treatment-resistant depression. The results of a much larger randomized trial (N = 1,167) are available and expected to be published, but patients younger than age 18 were excluded from this study. A retrospective study conducted in adult psychiatric patients found that patients whose treatment followed recommendations of a pharmacogenetic test including 20 genes were almost 4 times more likely to improve than patients whose treatment did not follow the recommendations.

### Table 2

**Antipsychotics: Pharmacogenetic guidelines and metabolizing enzymes**

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**Source:** References 3, 6, 7

*Guideline indicates whether there is a published guideline from the Dutch Pharmacogenetics Working Group (DPWG) or Clinical Pharmacogenetics Implementation Consortium (CPIC), or whether the FDA includes pharmacogenetic-related dosing recommendations on the drug label.

CYP2D6: cytochrome P450 family 2 subfamily D member 6

### Clinical Point

The FDA and DPWG recommend reducing the dose of aripiprazole in CYP2D6 poor metabolizers

continued
Pharmacogenetic testing at our pediatric inpatient unit

The Cincinnati Children’s Division of Child and Adolescent Psychiatry is the largest psychiatric inpatient service in a U.S. pediatric hospital. Starting in 2004, we adopted pharmacogenetically-guided dosing of psychiatric medications. CYP2D6 and CYP2C19 were chosen for testing because the enzymes encoded by these genes metabolize many of the antidepressants and antipsychotics that patients admitted to our unit will receive, and the clinicians wanted all available tools to help improve the care of these patients. To date, the Genetic Pharmacology Service (GPS) has performed >25,000 tests for variants in CYP2D6 and CYP2C19 as part of inpatient care. Patients provide a specimen (blood or buccal swab) at the time of admission to inpatient psychiatry, genotyping is performed onsite by the Molecular Genetics Laboratory (certified by the College of American Pathologists [CAP]/Clinical Laboratory Improvement Amendments [CLIA]) and the results are posted to the medical record within 2 business days. The report contains the patient’s alleles for CYP2D6 and CYP2C19, the genotype-predicted metabolizer phenotype, and dosing recommendations for 19 drugs (provided as a percentage of the standard dose). Insurance is billed for the test, and reimbursement is usually received when the test is performed as part of an inpatient stay.

The GPS team performed a retrospective chart review after the first panel was implemented in 2005. The study included 279 patients who were receiving a medication metabolized by one of the 2 genes tested. The poor metabolizers had the highest efficacy and highest number of adverse drug reactions, while ultra-rapid metabolizers had the lowest efficacy and lowest number of adverse reactions during their initial inpatient stay. In patients not treated with medications metabolized by CYP2D6 or CYP2C19, there was no association between metabolizer status and efficacy or adverse drug reactions. In this retrospective study, there was no association between metabolizer status and length of stay.

Overcoming the challenges

One challenge with many of the pharmacogenetic tests is interpretation of the results. The reports can span more than 20 pages, and clinicians may not have time to thoroughly read and understand how best to use all of this information. Sometimes the reports can make it seem like the first-line medication for the patient’s condition is not the best choice, but it could work well when dosed appropriately based on the patient’s genotype. Each commercially available test has a different way of presenting results, so when choosing a pharmacogenetic test, one should be sure to see a sample report. Vo et al recently reviewed factors to consider when choosing a pharmacogenetic test.

Because patients and families also have difficulty understanding the reports, we created patient education sheets, written at an eighth grade level with feedback from parents and modeled on those provided by St. Jude Children’s Research Hospital. St. Jude Children’s Research Hospital also has pharmacogenetic competencies that pharmacists and nurses must pass. The following is a sample explanation that one of our nurses uses to educate parents on what is being tested and what effect the results will have on the treatment plan.

“During your child’s stay we will be completing a genetic test to help us understand how he/she processes the types of medications that we may be likely to start during their hospitalization. This does not tell us which medication will be best—unfortunately within the field of psychiatry there is still some unavoidable trial and error; rather, what it will do is tell us how to make sure that the dosing is at a level that would be safe for the way your child’s body breaks down the medicine, so that he/she can get the intended benefit of the medicine’s effects, while decreasing the risk of uncomfortable side effects, where possible.”

Other challenges in pharmacogenetic testing are the cost, disease risk, and concern about how genetic information will be used. Because these tests are often not covered by health insurance, some commercial
pharmacogenetic testing companies offer an out-of-pocket maximum in the $250 to $350 range to reduce the cost to the patient. Some pharmacogenetic testing companies also test for genes associated with disease, so if a clinician orders the test, he or she may be responsible for sharing that information with the patient. For most pharmacogenetic testing companies, the turn-around time is 2 to 10 days. Genetic information is protected by federal laws, including Genetic Information Nondiscrimination Act (GINA) and Health Insurance Portability and Accountability Act (HIPAA).

The choice of psychotropic medication is complex, and although we would like pharmacogenetics to be the only answer to why every patient does or does not respond to a medication, it is not. Response to medication is influenced by age, comorbidities, illness severity, illness duration, compliance, gender, comitant medications, and potentially more. Pharmacogenetics is another tool at the clinician’s disposal to help in choosing a medication and dose. There is a clear association between CYP2D6 and CYP2C19 and exposure to many antidepressants and antipsychotics (reviewed by Stingl et al.); however, the link between exposure and response is much weaker. It may be strengthened by the inclusion of pharmacodynamic information (the level of expression of the drug target), which can be influenced by genetic variants. At the present time, the most evidence exists for testing CYP2D6 and CYP2C19, and the CPIC and DWPG guidelines provide evidence-based recommendations for how to adjust medication dosages based on the results.

There is clearly much more research that needs to be done in the field of neuropsychiatric pharmacogenetics, especially in pediatric populations. As we see increased utilization of pharmacogenetic tests in psychiatry, there is also a need for pharmacogenetic education of patients, families, nurses, pharmacists, and psychiatrists. Several good pharmacogenetic resources that contain up-to-date summaries of the available evidence linking pharmacogenetic variants to medication response, implementation resources, and educational resources are available. These include CPIC (www.cpicpgx.org), PharmGKB (www.pharmgkb.org), and the IGNITE Spark Toolbox (https://ignite-genomics.org/spark-toolbox/clinicians/).

Acknowledgements
The author thanks Jen Milau, APRN, for the case study and sample explanation, and Jeffrey Strawn, MD, FAACP, Ethan Powell, and Stacey Aldrich, MS, for help with preparing this manuscript.

References

## Bottom Line
Pharmacogenetically-guided dosing of psychiatric medications may help improve clinical outcomes, including for pediatric patients. Guidelines from the Clinical Pharmacogenetics Implementation Consortium and other organizations can help with interpretation of the results of pharmacogenetic testing.
Pharmacogenetic testing in children

Clinical Point
To reduce the cost to the patient, some testing companies offer a $250 to $350 out-of-pocket maximum


