UNIVERSITY OF WISCONSIN-MADISON SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Pharmacogenetic Testing in Psychiatric Pharmacy: Background, Clinical Relevance, and Barriers

by Sarah A. Fierek, 2022 PharmD Candidate, Amy M. Genisot, 2022 PharmD Candidate, Rachel A. Hawley, 2022 PharmD Candidate, Molly A. O'Connell, 2023 PharmD Candidate, Amy M. Wolff, 2023 PharmD Candidate

Pharmacogenetics is the study of how variations in inherited DNA sequences affect individual responses to medications.[1] Identifying gene variants is important, because variants can alter the pharmacokinetic and pharmacodynamic properties of drugs, thus impacting metabolism.

Approximately 1 in 5 prescriptions are affected by actionable pharmacogenes, meaning the presence of gene variants may influence how an individual responds to a medication.[2] Many psychotropic drugs, such as antidepressants, anxiolytics, and antipsychotics, are metabolized by enzymes that vary in activity based on one's genes. Although the use of medications affected by actionable pharmacogenes is common, preemptive pharmacogenetic testing is not yet widespread due to lack of access, affordability, utility, and necessity.[3]

Genes Targeted During Pharmacogenetic Testing

Cytochrome P450 (CYP) enzymes are responsible for the metabolism of many drugs. Namely, 90% of drugs are metabolized by six CYP enzymes: 1A2, 3A4, 3A5, 2C9, 2C19, and 2D6.[4] Genetic variability of CYP enzymes may lead to differences in how a patient responds to a particular drug. For example, a genotype that increases the activity of a CYP enzyme that metabolizes a drug will result in a lower concentration of the active drug in circulation, decreasing efficacy. Alternatively, a genotype that decreases the activity of a CYP enzyme that metabolizes a drug will lead to a higher concentration of drug in circulation, producing toxicity. Additionally, in the case of prodrugs, the effects on drug metabolism will be the opposite of those previously mentioned. That is, a genotype that induces metabolism of the prodrug will effectively result in an increase in active drug in circulation. However, a genotype that inhibits the metabolism of the prodrug will result in a decrease in active drug in circulation. This information has been incorporated into clinical practice guidelines to help clinicians predict how a patient will respond to a particular drug therapy.

Genotypes describe changes in the number of copies present of a gene encoding a functional CYP enzyme. In general, more functional copies of the gene result in an increased level of metabolism, while fewer functional copies of the gene result in a decreased level of metabolism. Using this idea, when individuals are genotyped, they can be placed into one of up to five phenotype groups. These groups are based on the number of functional copies of the gene they have, corresponding with the metabolic activity seen in their designated genotype. These groupings are: poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NM), rapid metabolizers (RM), and ultrarapid metabolizers (UM).[5] Individuals with two nonfunctional copies of a gene are considered poor metabolizers. There is little to no metabolic activity seen within this genotype. Individuals who have one functional copy of a gene and one nonfunctional copy are considered intermediate metabolizers. Within this group, there is more metabolic activity compared to the poor metabolizers, but less than in normal metabolizers. Individuals

TABLE 1. CYP Phenotypes[5]

Phenotype	*Example*	*Effect on Metabolism*
Poor Metabolizer (PM)	Individuals who are homozygous for a gene that results in a nonfunctional enzyme	Decreased activity of the enzyme resulting in little to no metabolism of the substrate
Intermediate Metabolizer (IM)	Individuals who are heterozygous for a gene that results in one functional copy and one nonfunctional copy of an enzyme	Decreased activity of the enzyme resulting in lower levels of metabolic activity than normal metabolizers, but greater activity than normal metabolizers
Normal Metabolizer (NM)	Individuals who are homozygous for a gene that results in two functional copies of an enzyme	Normal enzyme activity which results in normal levels of metabolism of the substrate
Rapid Metabolizer (RM)	Individuals who are heterozygous for a gene that results in one increased function copy and one normal function copy of an enzyme	Increased activity of the enzyme which results in an increased level of metabolism of the substrate
Ultrarapid Metabolizer (UM)	Individuals who have more than two functional copies of an enzyme	Increased activity of the enzyme which results in an increased level of metabolism of the substrate

who have two fully functioning copies of a gene are considered wild-type, and are normal metabolizers. They have what is considered normal metabolic activity of the enzyme. Lastly, those with genes conferring greater than normal level function (e.g., more than two functional copies of a gene) are described as rapid or ultrarapid metabolizers, depending upon the gene and level of activity. The metabolic activity of the enzyme for these groups is greater than that of the normal metabolizers. See Table 1 for a summary of the CYP phenotypes and their effects on substrate metabolism.

Clinicians should look to evidence-based guidelines created by organizations like the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Food and Drug Administration (FDA) for guidelines concerning prescribing medications with actionable pharmacogenes.[6,7] The CPIC and FDA provide information for over 200 medications and dosing guidelines regarding these drugs. These medications are used to treat many different disease states (i.e. anticoagulation, oncology, etc.) and involve a variety of CYP enzymes. However, only CYP2D6 and CYP2C19 provide clinicians with guidance for prescribing psychiatric medications within the CPIC guidelines.[6] These guidelines are specific for dosing of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). In terms of FDA guidelines, there are 40 neuropsychiatric medications with listed pharmacogenetic considerations.[7] For these 40 medications, information recommending that the dosage be modified if the patient has a known specific CYP variant and metabolizer status can be found in the package insert.[8] Pharmacists and clinicians often use additional resources that summarize pertinent dosing recommendations from CPIC and the FDA to increase efficiency during clinical encounters. One of these references is the *CPIC and FDA Labeling Guidelines Pocket Guide* created by Dr. Vincent Wartenweiler and Dr. Cody Wenthur, also published in this issue of *The Journal*.[9] This pocket guide contains information on genotypes, dosing recommendations based on phenotype, strength of recommendation, and additional information to note when dosing the given medication.

Clinical Relevance

Precision medicine is defined as targeting treatments to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from another with similar clinical presentations.[10] Advancement in precision medicine has led to improved clinical outcomes for specific patient populations. For example, precision medicine has been used in various disease states including cancer, cardiovascular disease, metabolic disease, smoking cessation, and psychiatry. The determination of treatment required for many of these disease states not only requires various biomarkers, but also genetic testing. Clinically actionable pharmacogenetic testing is used by clinicians to make prescribing recommendations when providing care to patients.[11] In practice, this testing has become more prevalent with one study of 11 million insured patients finding utilization to have nearly doubled between 2013 and 2017, increasing from 1,955 to 3,946 tests performed.[12]

For major depressive disorder, pharmacogenetic testing has the potential to reduce disease severity, decrease adverse drug reactions, improve response time to therapy, and provide cost savings to patients.[13] Further, studies of pharmacogenetic testing in other psychiatric conditions demonstrate evidence of clinical improvement with easy-to-administer tests and little risk to the patient.[14] Clinically, pharmacogenetic testing can be used in psychiatric patients when starting a particular medication to determine appropriate doses based on the patient's metabolic enzyme activity. Testing is also used in patients who have tried and failed multiple medication therapies, a common occurrence in psychiatric medications. Although the absolute utility of pharmacogenetic testing in psychiatry is still being determined, promising results for its use in specific patient populations were observed when analyzing adults less than 60 years old, diagnoses with moderate to severe depression, or diagnoses between 1 and 5 years in length.[15] Pharmacogenetic testing led to statistically significant reductions in

TABLE 2. Pharmacogenetic Resources

Resource	*Website Link*	*Description*
Clinical Pharmacogenetics Implementation Consortium (CPIC)[6]	https://cpicpgx.org/guidelines/	• This website provides clinical practice guidelines regarding how genetic test results can be used to optimize pharmacotherapy. • These guidelines are peer-reviewed and evidence-based.
Dutch Pharmacogenetics Working Group (DPWG)[26]	https://www.pharmgkb.org/page/dpwg	• This link provides access to the DPWG homepage. • DPWG provides a key describing how they rank evidence quality of a drug-gene interaction, as well as the clinical relevance of that interaction. • Through this website, specific clinical recommendations can be found on the KNMP website.
U.S. Food and Drug Administration (FDA)[7]	https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations	• This website links to the FDA's Table of Pharmacogenetic Associations. • This document highlights three categories of pharmacogenomic associations with currently approved medications.
Pharmacogenomics Knowledge Base (PharmGKB)[27]	https://www.pharmgkb.org/	• This website links to the homepage for PharmGKB. • There are annotations provided by PharmGKB for drug labels, clinical guidelines, curated pathways, and drugs. • The annotations can be used by clinicians and researchers to understand how genetic variation impacts drug response.

baseline depressive severity scores in patients with these characteristics when compared to adults of different ages, diagnosis, and diagnoses lengths.

Guidelines created by CPIC suggest how to apply the results of pharmacogenetic testing to tailor medication prescribing, but often lack recommendations on appropriateness.[11] Overall, more progress needs to be made in clinical studies comparing the use of prescribing guided by pharmacogenetic testing to medication decisions not guided by pharmacogenetic testing. This includes high-quality studies of adverse effect profiles and cost-effectiveness to prove clinical utility. With these improvements, clinicians will be provided with appropriate clinical guidance and reduced barriers to implementation to help guide psychiatric medication decisions.

Barriers to Pharmacogenetic Testing

The clinical implementation of pharmacogenetic testing in psychiatry has the potential to improve patient outcomes. However, many challenges exist concerning patient access to and provider execution of pharmacogenetic testing. In psychiatry, there is often a delay between a patient's treatment and their response to psychotropic medications.[16] Results from pharmacogenetic testing may optimize pharmacotherapy by maximizing therapeutic benefits and minimizing adverse effects for patients. Notable challenges for patients and providers in pharmacogenetic testing implementation in psychiatry include: cost-effectiveness; availability of resources and clinical guidelines; and provider preparedness.[16-19]

The cost-effectiveness of pharmacogenetic testing in psychiatry is not clearly defined, which has prevented widespread clinical implementation.[17] However, a systematic review of the utility of pharmacogenetic testing in psychiatry found five studies that evaluated cost-effectiveness.[18] Every study found a reduction in medical costs, ranging from 9.5% to 28%; these reductions were the result of fewer treatment failures and adverse events for patients. In addition, there is a lack of data regarding the availability of insurance coverage for pharmacogenetic testing. For patients with private insurance, coverage may vary depending on their insurance plan, the pharmacogenetic testing done, the lab completing the test, and the reason for testing.[20] The coverage of pharmacogenetic testing for Medicare and Medicaid beneficiaries can also vary based on a variety of factors, including necessity for testing and which gene is being analyzed.[21] To solve the insurance coverage barrier to testing, insurance companies must be provided with an incentive. This can be done by improving and expanding the current literature in pharmacogenetics to demonstrate that an upfront cost of pharmacogenetic testing can result in future savings for the insurance companies.[16]

Increased awareness of the clinical guidelines and other educational resources available to providers is important.[22] Mental health providers may include psychiatrists, nurse practitioners, primary care providers, or pharmacists under collaborative practice agreements. These clinicians, in addition to genetic counselors and other professionals, require training and support for pharmacogenetic delivery to be successful.[16] Research is currently underway to improve provider understanding of when pharmacogenetic tests should be ordered and how their results should be interpreted.[22] In 2018, a publication detailed the successful implementation of pharmacogenetic services in the inpatient psychiatry service over the course of 14 years at Cincinnati Children's Hospital Medical Center.[23] The use of a multidisciplinary team contributed to the success of implementing pharmacogenetic services, further proving the necessity of educating providers on pharmacogenetics.

Pharmacists, with their expertise in medication use, have the potential to serve as key resources in pharmacogenetics for both providers and patients.[19,24] In recent years, education for pharmacists on pharmacogenetics has increased. The Accreditation Council for Pharmacy Education (ACPE) 2016 Standards for the Doctor of Pharmacy curriculum require pharmacogenetics as an element of training.[25] In addition, practicing pharmacists can use the following resources, as mentioned previously, to improve their understanding of pharmacogenetics testing: CPIC, FDA, Dutch Pharmacogenetics Working Group (DPWG), and PharmGKB.[6,7,26,27] These resources are described in detail in Table 2.

Pharmacogenetic Spotlight

Marshfield Clinic Health Systems, Inc.

Some pharmacists in Wisconsin are using pharmacogenetic testing at their practice sites. One of these is Marshfield Clinic Health Systems, Inc., where Dr. Emili Leary, PharmD, specializes in pharmacogenetic testing and runs a pharmacogenetic bootcamp. The bootcamp (more formally known as the Marshfield Clinic Pharmacogenomics Certificate Program), started in 2018 and is a two-week, 80-hour intensive program. Throughout the program, participants learn about methods of DNA evaluation, and genes pertinent to pharmacogenetics. The participants engage in topic discussions, lectures, and clinical practice applications such as case studies. To make the experience more impactful and relatable, learners are offered the opportunity to complete and examine their own genetic test. Additionally, participants learn how to provide actionable recommendations based on pharmacogenetic test results to patients and providers. Currently, the program is offered to pharmacy residents, genetic counseling students, other internal Marshfield Clinic employees, and pharmacy students. In the future, the program will hopefully be expanded to include medical students and residents, as well as other professional students.

Clinically, Dr. Leary's job responsibilities include providing recommendations to practitioners after patients receive their pharmacogenetic test results. In practice, these genetic tests are used most often for disease states of anxiety and depression after multiple therapies have been ineffective or caused adverse effects. CYP2D6 and CYP2C19 are highly polymorphic drug metabolizing enzymes that can result in poor efficacy of psychiatric medications. In her practice, Leary's recommendations may include choosing a new medication that is not processed by those specific enzymes. Additionally, dosage adjustments can also be made. To help patients understand their results, Leary suggests that pharmacists use patient-friendly language and analogies.

Less than 1% of the clinic population at Marshfield Clinic uses pharmacogenetic testing. Cost is a significant barrier to these tests, with an average price around

$300-$400. After pharmacogenetic testing, 30-50% of patients have potentially actionable findings and may end up having their medication regimen modified. Marshfield Clinic is one of the first health systems to implement a pharmacist role in pharmacogenetic testing in Wisconsin; however, there is still room for expansion. Leary envisions that community pharmacies could use a patient's genetic results with the CPIC website to identify drug-gene interactions. Pharmacists would then be able to call the prescriber and intervene.

The work by Leary and her colleagues at Marshfield Clinic provides an excellent example of how pharmacogenetic testing can be implemented into practice to find more effective drug therapies for patients.

Sarah A. Fierek, Amy M. Genisot, and Rachel A. Hawley are 3rd Year Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Molly A. O'Connell and Amy M. Wolff are 2nd Year Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

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