Original Work

A Study of Routine Pharmacogenomic Testing in the Midwest Region: The Current State and Barriers Faced by the Field

by Kelsie E. Tingle, 2025 PharmD Candidate, Paul R. Hutson, PharmD, MS, Emili J. Leary, PharmD

Abstract

Objective: The purpose of this study was to survey major medical facilities in Wisconsin and nearby states about their typical use of pharmacogenomic testing in clinical practice.

Methods: Twenty healthcare systems in Wisconsin and the surrounding region were sent a questionnaire regarding which facilities were and were not implementing pharmacogenomics, along with which genes have been prioritized by those facilities that reported ongoing pharmacogenomic testing.

Results: Fourteen medical centers responded to the survey, and 10 facilities reported testing. Among the respondents, no two facilities tested for the same set of genes. Additionally, no single gene was tested for by all responding facilities.

Conclusions: Pharmacogenomic testing faces several barriers, which include evidence for clinical utility, cost effectiveness, and physician education and awareness. The lack of standardization across facilities implementing pharmacogenomics may be indicative of barriers faced by the field and institution-specific factors; the lack of standardization creates difficulties in comparing data between facilities due to inconsistencies in approach and in genes tested. Pharmacogenomics has the potential to lead to greater medication safety and efficacy, but its expansion would be aided significantly by additional clinician education and appropriate advocacy for the merits of pharmacogenomic testing, both in those facilities currently implementing and those seeking to do so.

Pharmacokinetics is an area of science that analyzes the impact of the body on a given drug over time, including absorption, distribution, metabolism and excretion. Pharmacodynamics, conversely, describes the effects of the drug on the body. As both of these processes are governed by complex processes including enzymes, transporters and receptors, genetic variation has the potential to result in significant differences in patient response to identical dosing regimens. A growing understanding of the relationships between gene and drug action or elimination is leading to the expansion of interest in incorporating pharmacogenomics into clinical practice. Pharmacogenomics is centered around the relationship between an individual's genes and their predicted response to a particular drug. Considering the variation between patients' genetic profiles allows for a personalized prediction of how those patients may differ in their response to a particular treatment given current evidence.

Clinicians must consider a wide variety of factors when determining the best medication and dosing for a given patient. These factors include age, lifestyle, disease states, allergies, and other medications. Based upon clinical judgement, a dose is then selected from a range of Food and Drug Administration (FDA) approved dosing for a given indication, which was determined by the design of pre-market clinical trials involving the response of a large pool of patients. Rather, the doses and regimens included in FDA approved labelling of the drug identify doses that are tolerable and effective for the majority of individuals, usually without consideration of an individual patient's pharmacogenomic profile. When used properly, pharmacogenomics provides an additional measure of safety and efficacy in its ability to individualize the treatment and potentially avoid a significant drug-gene interaction that would warrant a deviation from standard dosing and medication selection. This additional information decreases the chance that the patient will experience toxicities or therapeutic failure with their dosing regimen, allowing for improvements to safety, efficacy and optimal dosing.[1]

Pharmacogenomic testing typically follows one of two models: reactive or preemptive. Preemptive testing aims to obtain the genetic information necessary to determine pharmacogenomics-guided medication dosing in advance of the initiation of drug therapy. Reactive testing, conversely, typically occurs following an adverse drug reaction or a lack of therapeutic response as a method of identifying possible genetic causes for the unfavorable response to the drug regimen. To maximize the potential of preemptive testing, the patient's pharmacogenes are evaluated across many genes, providing information regarding numerous genetic variants, and the resulting data is stored using an electronic health record (EHR) for immediate as well as future application.

Ideally, these results would be used with clinical decision support (CDS) to generate alerts and suggested changes to the drug regimen when relevant interactions are identified.[2]

Several organizations have been founded to study and promote the incorporation of pharmacogenomics testing results into clinical decision-making. These include the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenomics Working Group, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), the French National Network of Pharmacogenetics (RNPGx) and the Pharmacogenomics Knowledgebase PharmGKB. PharmGKB is a National Institutes of Health (NIH)-funded resource that collects, curates and disseminates information about clinically actionable gene-drug associations.

Several innovative United States (US) institutions such as St. Jude Children's Research Hospital routinely obtain preemptive pharmacogenomics tests on children treated at their facility.[3] The Veterans Affairs Pharmacogenomic Testing for Veterans (PHASER) program provides free pharmacogenomics testing at participating Veterans Affairs (VA) medical centers, with additional sites being added.[4] The Ubiquitous Pharmacogenomics (U-PGx) consortium has implemented routine, pre-emptive pharmacogenomic testing in multiple countries in the European Union.[5] The NIH National Human Genome Research Institute supports clinical trials within the Implementing Genomics in Practice (IGNITE) Pragmatic Clinical Trials Network to develop clinical trials to establish clinical decision support tools to guide drug treatment adjustments.[6] Despite the growth and productivity of these collaborative efforts, implementation of routine pharmacogenomic testing in the US is not yet the standard of care. An important step towards incorporating pharmacogenomics as the standard of care is evaluation of the current landscape and status of pharmacogenomics testing. The purpose of this study was to survey major medical facilities in Wisconsin and nearby states about their use of pharmacogenomic testing in clinical practice, including which genes are tested by each facility.

TABLE 1. Examples of Genes with CPIC Guidelines

Gene	*Gene Function*	*Examples of Common Drugs Associated with Each Gene*	*Examples of Effects Related to Genotype*
CFTR	Drug Target Protein	Ivacaftor	Certain genetic variations of *CFTR* may prevent effective treatment by Ivacaftor by interfering with the drug's mechanism.
CYP2B6	Metabolism Enzyme	Efavirenz	Impaired *CYP2B6* function may increase the risk for CNS-related toxicities and discontinuation of treatment.
CYP2C9	Metabolism Enzyme	Phenytoin	Decreased function of *CYP2C9* can lead to higher plasma concentrations that contribute to increased risk of toxicities.
		Ibuprofen and other NSAIDS	Reduced function of *CYP2C9* may result in higher plasma concentrations which may increase the risk and severity of toxicities
CYP2C19	Metabolism Enzyme	Clopidogrel	Decreased function of *CYP2C19* can lead to suboptimal clopidogrel response and lead to higher risk of major adverse cardiovascular and cerebrovascular events compared to treatment with other antiplatelet therapies.
		Citalopram and other SSRIs	Impaired *CYP2C19* function can result in higher plasma concentrations which may increase the probability of side effects.
CYP2D6	Metabolism Enzyme	Codeine	Increased *CYP2D6* function can lead to increased formation of morphine, resulting in a greater risk of toxicity. Reduced *CYP2D6* activity can lead to decreased morphine formation and diminished analgesia.
		Paroxetine and other SSRIs	Impaired *CYP2D6* function can result in higher plasma concentrations which may increase the probability of side effects.
		Ondansetron	Increased *CYP2D6* function can lead to increased metabolism, associated with decreased efficacy.
DPYD	Metabolism Enzyme	Capecitabine Fluorouracil	Reduced *DPYD* function can lead to increased risk for severe/potentially fatal drug toxicity with fluoropyrimidine drugs.
G6PD	Toxicity Mediator Enzyme	Rasburicase	*G6PD*-deficiency results in a greater risk for acute hemolytic anemia.
HLA-A	Immune System Recognition Protein	Carbamazepine	The HLA-A*31:01 positive genotype results in a greater risk of carbamazepine-induced Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, as well as drug reaction with eosinophilia and systemic symptoms or massive pulmonary embolism.
HLA-B	Immune System Recognition Protein	Carbamazepine Phenytoin Oxcarbazepine	The HLA-B*15.02 positive phenotype results in an increased risk for drug-induced Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.
		Allopurinol	The HLA-B*58:01 phenotype significantly increases the risk of allopurinol-induced severe cutaneous adverse reactions.
		Abacavir	The HLA-B*57:01 phenotype results in a significantly increased risk of abacavir hypersensitivity.

Methods

Twenty healthcare systems in Wisconsin and neighboring states were sent a questionnaire in the spring of 2022. In some cases, the survey was forwarded from the original contact to a different individual for completion. The survey asked which facilities were and were not implementing pharmacogenomic testing, along with which genes were tested. The survey questioned facilities about 14 genes, each of which has clinically actionable guidelines provided by CPIC (Table 1). The list of genes of pharmacogenomic interest considered in this study was not exhaustive, but rather consisted of genes with strong evidence to support prescribing decisions based upon genetic information. In total, 14 genes and the drug pairs they are associated with were displayed alongside examples of genotype-associated risks reported in CPIC guidelines.[7–21] The information reported by the surveyed facilities was compared and displayed. Facilities were additionally given the opportunity to disclose additional genes offered in their pharmacogenomic testing panels. A reminder email was sent with a link to the survey to institutions that did not respond to the initial request. Institutional Review Board exemption was obtained from the University of Wisconsin-Madison.

TABLE 1. Examples of Genes with CPIC Guidelines - Continued

Gene	*Gene Function*	*Examples of Common Drugs Associated with Each Gene*	*Examples of Effects Related to Genotype*
IFNL3/ IFNL4	Unclear Mechanism	Ribavirin	Individuals carrying the unfavorable response allele, or the T allele, have a decreased likelihood of response, or a lower systemic vascular resistance rate to therapy with ribavirin.
		Peginterferon alfa-2a	Individuals carrying the unfavorable response allele, or the T allele, have a decreased likelihood of response, or a lower systemic vascular resistance rate to therapy with peginterferon alfa-2a.
NUDT15	Metabolism Enzyme	Azathioprine Mercaptopurine	A decrease in function of NUDT15 increases the risk of thiopurine-related leukopenia, neutropenia and myelosuppression.
SLCO1B1	Transporter Protein	Atorvastatin Simvastatin	Decreased SLCO1B1 function may lead to increased risk of myopathy due to increased atorvastatin and simvastatin exposure.
TPMT	Metabolism Enzyme	Azathioprine Mercaptopurine Thioguanine	Decreased TPMT function may lead to high concentrations of TGN metabolites, contributing to toxicity which may lead to leukopenia, neutropenia, myelosuppression, or death.
UGT1A1	Metabolism Enzyme	Irinotecan	Impaired function of UGT1A1 may lead to a greater probability of toxicity.

CPIC = Clinical Pharmacogenetics Implementation Consortium; CNS = central nervous system; NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor

TABLE 2. Tested Pharmacogenomic Genes of Interest Reported by Surveyed Facilities

Facility	Children's Wisconsin	Mayo Clinic	St. Jude Children's Research Hospital	University of Illinois Hospital	William S. Middleton Memorial Veterans Hosptal	Children's Minnesota	Gundersen Health System	Marshfield Clinic Health Systems	Indiana University School of Medicine	Michigan Medicine
CYP2D6		✓	✓		✓	✓		✓	✓	
CYP2C19		✓	✓	✓	✓	✓		✓	✓	✓
CYP2C9		✓	✓	✓	✓	✓		✓		✓
CYP2B6			✓			✓		✓		
TPMT	✓	✓	✓		✓	✓	✓	✓	✓	✓
DPYD		✓	✓		✓	✓	✓	✓	✓	✓
UGT1A1		✓	✓			✓	✓	✓	✓	✓
NUDT15	✓	✓	✓			✓	✓	✓	✓	
HLA-B		✓				✓		✓	✓	✓
HLA-A		✓				✓		✓		
SLC01B1		✓	✓		✓	✓		✓	✓	
CFTR	✓					✓			✓	
G6PD			✓			✓	✓		✓	✓
IFNL3/IFNL4					✓	✓			✓	

Results

Fourteen of the 20 medical centers contacted for this survey responded. Of the 14 healthcare systems responding, seven were institutional facilities affiliated with Big Ten universities, while the other seven participants were regional health systems and hospitals. Four facilities reported that pharmacogenomic testing was not incorporated into their patient care process. The responses from the remaining 10 facilities can be seen in Table 2. Notably, only one of these 10 facilities reported pharmacogenomic testing for all 14 genes included in the survey. No two facilities were observed to test for the same panel of genes when considering the additional genes reported by facilities (Table 3).

It is notable that no one gene was tested by every responding facility. Nine facilities reported testing for *TPMT* for patients receiving thiopurines, eight facilities reported testing for *CYP2C19*, and a different set of eight facilities reported testing for *DPYD* for patients receiving 5-fluorouracil. Genes that were less commonly reported included *HLA-A*, which was only tested for at three of the responding facilities. *IFNL3/IFNL4*, *CFTR* and *CYP2B6* were only reported by four facilities each.

Discussion

Despite the routine use of pre-emptive pharmacogenomic testing in many United States VA medical centers[4], and in some European countries, pre-emptive testing is not commonly or consistently employed, as was observed in our survey results. Commonly cited barriers to pharmacogenomic implementation include lack of evidence for clinical utility, lack of evidence for cost effectiveness, and lack of physician education and awareness.[22] Clinical utility of pharmacogenomic testing has been questioned due to a lack of randomized controlled trials (RCTs), which are generally considered the gold standard for considering new interventions or tests. Legitimate concerns exist about the use of RCTs in evaluating pharmacogenomics, as randomizing patients who carry known and actionable pharmacogenomic variants to treatments known to be suboptimal or even harmful would be unethical.[23]

Cost-effectiveness evaluations of pharmacogenomics are influenced by a wide variety of factors including the site at which testing occurs (e.g., institutional billing model considerations, specialty focus, etc.), whether the test is performed by a commercial vendor or on-site at the facility (e.g., consideration of patient assistance programs, platform used, etc.), and whose perspective is being evaluated in the cost-effectiveness evaluation (e.g., societal, health system, payer or patient perspectives). Cost effectiveness evaluations are further complicated by widely variable reimbursement (e.g., federal vs commercial insurers and associated caveats). There is not currently widespread insurance coverage for pharmacogenomic testing. When full or partial reimbursement is available, however, it can play a significant role in the decision to pursue pharmacogenomic testing, influencing both the physician and the patient.[22] A significant difference is observed in the accessibility of germline and somatic pharmacogenomic testing due to lack of coverage for germline variants. In contrast to the reimbursement struggles faced by germline pharmacogenomic testing, tumor/biopsy testing for actionable somatic mutations is more likely to be covered by medical insurance.[24]

A lack of physician education presents another significant challenge to overcome in clinical implementation of pharmacogenomic testing; it is generally the physician who advocates for the testing and is responsible for ordering the test for the patient at implementing facilities as pharmacists often do not have the authority to order testing without a collaborative practice agreement (CPA) in place. Without advanced training in pharmacogenomic testing including test benefits, risks and limitations, it may be challenging for physicians to utilize pharmacogenomic testing appropriately and to its full potential. The lack of trained and/or experienced personnel in pharmacogenomics may explain why many facilities are hesitant to initiate or expand pharmacogenomic testing. In a 2012 survey of physicians that were board-certified in family or internal medicine, Haga et. al. found that 306 of 597 respondents, or more than half of those surveyed, felt they were not properly informed about how to

TABLE 3. Additional Pharmacogenomic Genes of Interest Reported by Surveyed Facilities

Facility	Children's Wisconsin	Mayo Clinic	St. Jude Children's Research Hospital	University of Illinois Hospital	William S. Middleton Memorial Veterans Hospital	Children's Minnesota	Gundersen Health System	Marshfield Clinic Health Systems	Indiana University School of Medicine	Michigan Medicine
Additional Genes Reported		NAT2, CYP3A4, CYP3A5, CYP1A2, VKORC1, CYP4F2, CYP2C cluster (rs12777823), HTR2A, HTR2C, COMT, DRD2, CHRNA3, EPHX1, GRIK4, OPRM1, SCN1A, UGT2B15, ANKK1, ADRA2A, SLC6A4, MT-RNR1	mt-RNR1, CACNA1S, RYR1, CYP3A5		CYP2C, CYP3A5, CYP4F2, VKORC1	RYR1/CACNA1S-MHS, CYP3A5 - Tacrolimus, CEP72-VIPN (research), CYP4F2/VKORC1 (not using clinically at this time), F2, F5		CYP3A4, CYP4F2, F2, F5, VKORC1		

interpret pharmacogenomic test results. Another 131 respondents denied receiving any education on the subject, and 435, or almost three quarters of the physicians, did not feel qualified to use pharmacogenomic tests or to interpret the results.[22,25] A more recent survey of physicians conducted by Smith et. al. in 2020 had similar findings, noting that only 26% of physicians surveyed felt confident using pharmacogenomic results for clinical decision-making. The same study also found that 70% of providers wanted a pharmacist consultation for help interpreting pharmacogenomic results.[26]

Another factor that may influence a facility's ability to expand their testing is the laboratory with whom they contract for testing. Facilities that test in-house may have more flexibility in which genes/genotypes they choose to test for, depending upon the platform and technology they utilize. Whole genome sequencing (WGS) is not the standardized method for pharmacogenomic testing at this time due to upfront cost as well as data processing and storage concerns, so most pharmacogenomic testing only queries variants that have been identified and specifically screened for (e.g., genotyping). Other variants that are not known or specifically assessed will be missed, leading to incorrect categorization of genes as "wild-type" in the reported results, regardless of whether their impact on metabolism matches that of the wild-type state.[27] Thus, if a vendor does not test for certain low frequency variants in a particular gene, the reported results may incorrectly indicate a normal, wild-type genotype.[28] Similarly, the genes each facility reported testing for may reflect the genes routinely tested by their third-party vendor. The vendor selection may be influenced by factors including (but not limited to) the primary indication for testing, patient cost, institutional contract pricing, gene offerings and coverage of genes labeled actionable by CPIC and the FDA, and integration of results into the medical record, with or without Clinical Decision Support (CDS) interface.

Limitations of this study exist, in addition to those inherent in survey research (e.g., biased nature of solicited responses and targeted demographic, etc.). Although several institutions affiliated with the Big 10 Academic Alliance along with select other healthcare systems across the state of Wisconsin were included in this survey, the list was not inclusive. Additionally, not all facilities had a clear point of contact listed for pharmacogenomic testing; thus, it was difficult to identify the most appropriate individual to receive the current survey for each facility; at times the survey was forwarded from the original recipient to another individual within the organization to complete the survey. This lack of clarity in identifying the most relevant expert in pharmacogenomics for a facility reflects the growing nature of the field, as pharmacogenomic testing is not yet prevalent or consistently applied. This may have impacted the generalizability of the results, as the data presented is only as accurate as the data that was reported through the questionnaire; notably, this also speaks to the need for more experts in the field.

Conclusion

Pharmacogenomic testing has been recognized as a useful tool to improve drug regimens in some clinical centers. Just as genetic testing of biopsied tumors is used to identify the somatic mutations associated with cancers to help optimize treatment, germline pharmacogenomic testing can be used to avoid potentially harmful treatments and, in some cases, optimize dosing. We found that pharmacogenomic testing is not standardized across different facilities in Wisconsin's region: some health care systems are implementing pharmacogenomic testing to varying extents, with others not yet implementing it at all. Improved sharing of best practices to identify and overcome barriers by facilities will be important in expanding routine pharmacogenomic testing, and it might encourage other facilities to begin implementing routine pharmacogenomic testing.

When considering the lack of standardization across facilities, two possibilities arise for future consideration. First, the lack of consistency in genes may be representative of different barriers faced by different healthcare systems, as well as institution-specific factors like the primary demographic served by that institution (e.g., institutions that focus on cancer may focus testing on genes more pertinent for oncology, namely *DPYD* and *TPMT*, versus another institution that focuses more on genes like *CYP2C19* and *SLCO1B1* for cardiology). Another possibility is that the lack of standardization itself may be a barrier to further implementation by making it difficult to track health outcomes of pharmacogenomic testing across different facilities. Next steps in advancing pharmacogenomic testing throughout the region may include evaluating the barriers to engaging in pharmacogenomic testing and directly querying which factors impacted selection of genes for each surveyed facility, as well as obtaining improved cost-utility data from the EHRs of participating facilities.

It is also vital to further clinician education in the area of pharmacogenomics by expanding the precision medication and genetics education provided in both medical and pharmacy schools, as well as offering and promoting more continuing education opportunities in the area of pharmacogenomics. More widely available offerings such as pharmacogenomics certificates, courses and continuing education offerings would help address the lack of education. One additional strategy would be for pharmacists to attain provider status, allowing for expanded roles in the implementation of pharmacogenomic services. As demonstrated by Smith et. al[26], many physicians prefer to consult a pharmacist and rely on the pharmacist's expertise in interpreting pharmacogenomic test results. Shifting patient identification, ordering, interpretation and follow-up duties to pharmacists would more efficiently and effectively allow incorporation of pharmacogenomic testing in routine clinical practice. Advocacy by clinicians (both physicians and pharmacists) will also be important for the adoption of pharmacogenomic tests in facilities that are not yet implementing a pharmacogenomic testing program.

Pharmacogenomic testing helps healthcare professionals provide patients with safer and more precise medication dosing, and in some cases more efficacious therapy selection. Of 14 queried facilities in the Upper Midwest and Big 10 network of schools, 10 facilities reported testing, and of those 10, no two facilities reported testing for the same set of genes. This lack of standardization across institutions may be considered a commentary on the barriers and challenges faced by facilities engaged in pharmacogenomic testing, as well as a

potential barrier itself due to the difficulty of compiling results among facilities that have different health outcomes resulting from different sets of genetic results. To address these challenges and to advance the field of pharmacogenomics, it is necessary for both pharmacists and clinicians to be educated on, and advocate for appropriate testing.

Kelsie Tingle is a 2025 Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Paul Hutson is a Professor at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Emili Leary is a Research, Clinical, MTM and Outpatient Pharmacist at Marshfield Clinic Research Institute – Center for Precision Medicine Research Institute in Marshfield, WI.

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Corresponding Author:
Paul Hutson - paul.hutson@wisc.edu

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