

The Role of Pharmacogenomic Biomarkers in Predicting and Improving Drug Response

Part 2: Challenges Impeding Clinical Implementation

C. Lee Ventola, MS

This is the second article in a two-part series about pharmacogenomics and drug response. Part 1 discussed the clinical significance of pharmacogenetic variants in the September 2013 issue of *P&T*.

Introduction

Clinical studies have identified many pharmacogenetic variants that influence drug response and treatment outcomes.¹⁻⁴ To date, significant gene–drug associations have been defined for many medications, including widely used cardiovascular, cancer, anticonvulsant, opioid, and proton pump inhibitor treatments.^{1,3-8} However, despite a growing awareness of pharmacogenetic data and its inclusion in revised product labels by the FDA, the clinical application of this information has been slow.⁹ This is because many hurdles exist that limit or obstruct the application of this information in clinical practice, including inconsistent study results; lack of prescriber education; reimbursement restrictions; and ethical, legal, and social concerns.^{3,7}

The clinical application of pharmacogenetic data has been slow.

Key factors that will encourage the successful clinical implementation of pharmacogenetic data include the development of clinical guidelines to ensure consistent interpretation and prescribing practices, as well as evidence-based information databases and educational programs to support decision-making.¹ Many consortiums and other organizations have been established to pursue these goals in order to advance the clinical adoption of pharmacogenomics.⁵

Factors Impeding the Clinical Application of Pharmacogenetics

Insufficient Validation of Study Results

Large amounts of pharmacogenetic data have been published; however, most of the data have not yet been applied clinically.^{2,5} Although some of the data have been adequately verified, this lack may be due, in part, to the paucity of reproducible study results for other pharmacogenetic gene–drug associations, as well as to the questionable utility of findings observed in small or specific populations.^{4,5,8}

The common benchmark required for research results to be considered valid is typically a large-scale, prospective, randomized controlled clinical trial, yet this study design is often not practical for testing pharmacogenetic hypotheses.⁹

To have sufficient statistical power, pharmacogenetic studies must stratify subjects equally across all groups.³ However, this cannot often be achieved for pharmacogenetic clinical studies, because many variant alleles occur in a population at a frequency of only 1% to 2%.³ The low prevalence of a specific variant allele in a population causes numerous pharmacogenetic studies to be conducted with very small sample sizes.³ This situation increases the probability of errors resulting from a lack of sufficient statistical power, so results from such studies might not be accurate.³ Alternative evidence-gathering strategies, therefore, may often be required, such as innovative clinical trial designs, the incorporation of pharmacogenomic testing into drug-development programs, and postmarketing observational studies.⁹

The difference in genetic makeup among ethnic populations is another factor that may prevent reproducible study results.⁸

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Pharmacogenomic studies often enroll populations in wealthier countries; this practice limits the usefulness of these results when treating patients in developing countries who differ genetically.⁵ Variability in the results of pharmacogenomic studies may also be due to epistasis (gene–gene and gene–environment interactions); epigenetics (non–DNA sequence-related heredity); or other genetic factors, which are largely unexplored in pharmacogenomic research.^{2,10} Most pharmacogenomic traits are also likely to be polygenic in nature; therefore, quite a bit of additional research is necessary to adequately define these characteristics in a way that is clinically useful.^{2,10}

Cost

An additional barrier that impedes the clinical utilization of pharmacogenetic testing is cost. Many physicians currently consider the expense of genotyping as outweighing its potential benefits.⁵ However, this notion might be inaccurate. For example, a recent mathematical modeling study showed that using genotype-guided clopidogrel therapy was more cost-effective for some patients than prescribing this drug (or its alternative, prasugrel) for all candidates.⁵

Another challenge limiting the clinical utility of pharmacogenetic testing is that the identification of a genetic variant that predicts a predisposition to an exceedingly rare adverse drug effect may have such a low positive predictive value that screening might not be considered worthwhile or cost-effective.⁴ There may therefore be only a limited number of agents for which the incidence of heritable genetic effects is large enough, the therapeutic index low enough, and treatment costs high

The author is a consultant medical writer living in New Jersey.

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enough that genetic testing becomes advisable.⁴

Several reports have attempted to systematically evaluate the pharmacoeconomics of genetic testing for specific treatments;

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those studies relating to warfarin concluded with significant uncertainty in economic value, and high commercial genotyping expenses were a major contributor to cost-ineffectiveness.⁴ However, the rapid decline in genotyping costs is quickly causing the results of many cost-effectiveness studies to become outdated.⁹ As gene-sequencing costs continue to fall, the debates surrounding expense will soon become moot.^{4,6} Increased drug efficacy, as well as decreased morbidity and mortality rates, is expected to occur as a result of pharmacogenetic testing, potentially leading to immense costs savings in health care.⁵

Clinician Education

Another barrier that impedes the more widespread clinical use of pharmacogenetic data is a need for trained doctors and pharmacists with adequate expertise in interpreting pharmacogenetic test results.⁵ A recent survey indicated that a lack of physician awareness regarding evidence-based pharmacogenetic data is a major challenge.^{3,5}

In another study, 80% of pharmacist respondents disagreed when asked if pharmacogenomics was an integral part of the curriculum at the pharmacy schools they had attended.³ Other recent surveys indicated that many pharmacists and physicians in the U.S. felt inadequately educated about pharmacogenomics.¹ By contrast, additional studies show that health professionals who received instruction in pharmacogenomics as part of their formal education felt well informed and were often early

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adopters of pharmacogenetic testing.¹

Specific knowledge gaps concern the pharmacogenetic tests available, how to procure them, and how to interpret and apply the results to patient care in the context of other clinical variables. The end result of this deficiency is that drugs are often prescribed to patients whose relevant genotype is unknown.¹ For example, codeine is a prodrug that is converted to its active metabolite, morphine, by cytochrome P450 (CYP) enzymes encoded by the *CYP2D6* gene.^{1,3} In the absence of genetic test results, codeine is still routinely prescribed to patients even though there is strong evidence that those who have genetic *CYP2D6* variants, causing them to be poor codeine metabolizers, are not likely to experience analgesia, whereas patients with genetic variants for ultra-rapid metabolism are at increased risk for opioid toxicity.¹

Reimbursement

The clinical utilization of pharmacogenetic testing also relies on reimbursement by private and public third-party payers.⁶

However, the health care reimbursement climate is constantly changing, and insurance coverage for pharmacogenetic testing currently varies.⁹ Pharmacogenetic testing will need to demonstrate consistent clinical utility and cost effectiveness before it is widely considered to be eligible for reimbursement.⁹

In 2009, the Centers for Medicare & Medicaid Services

Increased drug efficacy and decreased morbidity and mortality rates may eventually lead to immense cost savings in health care.

(CMS) determined that genetic testing for *CYP2C9* and *VKORC1* genes to determine warfarin response was neither reasonable nor necessary.⁹ This decision was made despite the availability of FDA-approved pharmacogenetic tests and statements in the product information that highlighted the importance and influence of *CYP2C9* and *VKORC1* genetic variants on proper warfarin dosing.⁹ Instead, the CMS announced a “coverage with evidence development” strategy in which pharmacogenetic testing would be eligible for reimbursement only when a warfarin-naive patient is enrolled in a prospective, randomized controlled clinical trial.⁹ Because the reimbursement policies that CMS adopts often influence private third-party payers, most insurers are awaiting the results of ongoing prospective warfarin pharmacogenetic clinical trials before approving reimbursement for *CYP2C9* and *VKORC1* genetic testing.⁹

In today’s challenging economic environment, fiscal restraint is a top priority for both health care payers and practitioners.¹ It is therefore important for future pharmacogenomic clinical trials to include pharmacoeconomic assessments.⁹ To this end, pharmacy benefit managers, including Medco, have partnered with health care organizations, such as the Mayo Clinic, to determine the benefits of modifying pharmacotherapy on the basis of genotyping.¹ Such a partnership found that the *CYP2C9* and *VKORC1* genotyping of new warfarin recipients resulted in a 43% lower risk of hospitalization for bleeding or thromboembolism.¹

Privacy and Information Management

The increasing number of clinically relevant pharmacogenetic variants will soon far exceed the capacity of a clinician’s memory as well as his or her ability to integrate these variants into clinical decision-making.¹ Fortunately, the difficulties of reporting, organizing, and interpreting complex pharmacogenetic test results will be alleviated by the continued adoption of electronic medical records.¹ Full clinical utilization of pharma-

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cogenetic information will require a curated, updated database of evidence-based gene–drug associations that is available for physicians to use in their medical practice.⁶ This resource will be especially useful when the sequenced genomes of all indi-

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viduals are readily accessible for physician review.⁶ However, despite the expected utility of this information, privacy concerns regarding the electronic tracking of an individual's genetic data represent another obstacle that impedes the routine application of pharmacogenetics in clinical practice.⁵

Efforts to Advance the Clinical Application of Pharmacogenomics

Development of Clinical Practice Guidelines

Many consortiums have been established for the purpose of advancing the clinical adoption of pharmacogenomics.⁵ One ongoing effort by the consortiums is to develop peer-reviewed clinical practice guidelines for interpreting and applying pharmacogenetic test results.^{1,9} Some of these consortiums and their work are described in this section. A listing of consortiums, as well as other sources of information about pharmacogenomics, is presented in Table 1.

In 2009, the Clinical Pharmacogenomics Implementation Consortium (CPIC) was formed as a shared project between the National Institutes of Health's Pharmacogenomic Research Network (PGRN) and The Pharmacogenomics Knowledgebase (PharmGKB), in order to resolve issues impeding the clinical implementation of pharmacogenomics.⁵ The CPIC regularly

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publishes evidence-based, peer-reviewed guidelines based on gene–drug associations in *Clinical Pharmacology and Therapeutics*.⁹ To date, this consortium has developed guidelines for many gene–drug pairs, including *HLA-B*–abacavir, *CYP2D6*–codeine, *TPMT*–thiopurines, *CYP2C9*–warfarin, *VKORC1*–warfarin, and *CYP2C19*–clopidogrel.⁵ Evidence-based practice guidelines have also been developed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, which was launched by the Office of Public Health Genomics at the Centers for Disease Control and Prevention.⁹

The International Warfarin Pharmacogenetics Consortium (IWPC) has developed a pharmacogenetic algorithm to estimate warfarin dosing.⁴ This guideline was shown to produce dosing recommendations that were significantly closer to the required stable therapeutic dose compared with an algorithm based only on phenotypic parameters or a fixed-dose strategy.⁴ The pharmacogenetic algorithm correctly predicted low doses for 54% of all patients; by contrast, the clinical algorithm predicted low doses for only 33%.⁴ The pharmacogenetic algorithm also accurately predicted high doses for 26% of the patients who required them, compared with 9% for the clinical algorithm.⁴ Therefore, the pharmacogenetic algorithm significantly improved the dose prediction for patients at the extreme ends of the dosage distribution, a group representing 46% of the entire cohort.⁵ This strategy is also likely to be applied to other commonly prescribed drugs that display individual variability in drug response and/or a narrow therapeutic index.⁴

The Personalized Medicine Coalition (PMC) was launched in 2004 to advance personalized medicine as a solution to the

Table 1 Resources for Pharmacogenomic Information

Consortiums and Coalitions

Clinical Pharmacogenomics Implementation Consortium (CPIC)
www.pharmgkb.org/page/cpic

Pharmacogenomic Research Network (PGRN)
www.nigms.nih.gov/Research/FeaturedPrograms/PGRN/

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
www.egappreviews.org/

International Warfarin Pharmacogenetics Consortium (IWPC)
www.pharmgkb.org/page/iwpc

The Personalized Medicine Coalition (PMC)
www.personalizedmedicinecoalition.org

The International HapMap Consortium
<http://hapmap.ncbi.nlm.nih.gov/>

1000 Genomes Project Consortium
www.1000genomes.org/

Pharmacogenomic Databases

Pharmacogenomics Knowledgebase PharmGKB
www.pharmgkb.org

Pharm ADME Core Gene List (absorption, distribution, metabolism, and excretion)
www.pharmaadme.org/joomla

The National Center for Biotechnology Information Gene Expression Omnibus (GEO)
www.ncbi.nlm.nih.gov/geo

Educational Programs

PharmGenEd
<http://pharmacogenomics.ucsd.edu/about-us/pharmgen-ed-objectives.aspx>

Continuing Education Programs
(numerous online sources)

Data from references 1, 3–5, and 9.

challenges of drug efficacy, safety, and cost.⁵ Further information on personalized medicine-based initiatives pursued by this group can be found at the PMC Web site listed in Table 1.⁹

The possibilities for pharmacogenomic research have also greatly expanded because of data generated by the International

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HapMap and the 1000 Genomes Project Consortia.¹ The International HapMap Project has constructed a high-density haplotype map of the human genome, which provides an important tool for studying complex phenotypes, such as drug response, in different racial or ethnic populations.¹ Established in 2008, the 1000 Genomes Project is an international public-private consortium that aims to build a detailed map of human genetic variation, ultimately including data from the genomes of more than 2,600 people from 26 populations worldwide.¹

Establishment of Evidence-Based Databases

An important initial step toward the clinical application of pharmacogenetic data involves the storage and dissemination of information in a curated database.⁶ In an effort to organize and summarize data regarding important pharmacogenetic variants, several organizations have prepared curated gene lists that are based on the published literature.⁹ For example, PharmGKB manages a public Web site for use by clinicians and researchers that curates information about the effect of pharmacogenetic variants on drug response.⁵ The Very Important Pharmacogene (VIP) summaries, compiled by PharmGKB, are a thorough and important resource, as is the Core Gene List, published by PharmADME.⁹ Today, the curators at PharmGKB have noted evidence that more than 2,000 genes are involved in drug response.⁴

Researchers also use *in silico* methods to analyze genomic databases to predict new uses for existing drugs.¹ Data from the 1000 Genomes Project includes DNA sequencing results from approximately 1,700 people; data from another 900 samples are expected to be added soon.¹ Another public source of data is the National Center for Biotechnology Information Gene Expression Omnibus (GEO), a public repository that archives and provides access to microarray sequencing and other forms of high-throughput functional genomic data submitted by researchers.¹

Health care professionals are expected to play an increasingly important role in encouraging health care systems to actively participate in the emerging field of pharmacogenomics.

Two studies identified cimetidine as a possible candidate therapy for lung adenocarcinoma, based on gene expression data accessed from the GEO database.¹ Results of follow-up preclinical studies subsequently validated the efficacy of cimetidine in treating this condition.¹

Several potential treatments for inflammatory bowel disease were also identified *in silico*, with the antiepileptic drug topiramate identified as a potential candidate.¹ The efficacy of topiramate was subsequently validated in a preclinical rodent model of colitis.¹ These reports provide proof-of-principle that analysis of public gene expression databases is a resourceful and affordable strategy for discovering possible new uses for approved drugs.¹ This approach may provide a more efficient and cost-effective alternative to traditional drug discovery methods.¹

Educational Programs

Health care professionals are expected to play an increasingly important role in encouraging health care systems to actively participate in the emerging field of pharmacogenomics. Therefore, physicians and pharmacists need to become familiar with the translation of pharmacogenetic information into clinical practice.³ Several evidence-based online educational resources are available for this purpose.³ The PharmGenEd program is designed to provide physicians, pharmacists, and other health professionals access to evidence-based pharmacogenetic information.³ The objective of PharmGenEd is to help health care professionals increase their awareness and knowledge about the validity of pharmacogenetic tests and their potential clinical implications.³ Included among the educational materials that PharmGenEd provides are interactive case studies, which are designed to be directly relevant to clinical practice.³

Utilizing a “train-the-trainer” approach, PharmGenEd also distributes educational materials about pharmacogenomics to qualified speakers and educators.³ Continuing medical education programs for clinicians are also available at many national, regional, and local professional meetings as well as on the Web.³

Conclusion

Despite rapidly accumulating data showing the influence of genetic variation on drug response, the clinical application of these evidence-based findings is still limited.⁵ As genotyping technology becomes more advanced, affordable, and accessible, findings from future studies will ideally provide more consistent results.⁸ After the clinical utility of predictive pharmacogenetic testing is better established, it will likely become more widely used.⁸ However, this can occur only with the support and involvement of clinicians, regulatory organizations, and public and private third-party payers.¹⁰ Although participation has not been occurring nearly as rapidly as the speed at which pharmacogenomic technologies are advancing, all parties are at least taking incremental steps toward the goal of incorporating clinical pharmacogenetic testing into routine patient care.

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