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Pharmacists should jump onto the clinical pharmacogenetics train

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This issue of *AJHP* is a theme issue on precision medicine, focusing on the use of pharmacogenetics in the clinical setting. The articles included provide substantial insight on how and why pharmacogenetics might and can be implemented in the clinical setting. In the past three to five years, the number of institutions undertaking such implementations has steadily increased, so concrete examples are now available. The opportunity that clinical pharmacogenetics presents for pharmacists is substantial, and ASHP is to be commended for taking a leading role to help advance the profession's stake in this important aspect of healthcare.

The term *pharmacogenetics* was first coined in the 1950s, with the discoveries of genetic variations in plasma cholinesterase activity and their effect on patients' response to succinylcholine, genetic variability in the genes encoding *N*-acetyltransferase that contributed to toxic responses to isoniazid, and the presence of glucose-6-phosphate dehydrogenase deficiency among patients experiencing hemolytic anemia after receiving primaquine.[1] Sixty years have passed since there was an appreciation for inherited differences in drug responses, based on similarities observed within families and differences between specific populations (e.g., those of European versus Asian versus African ancestry). However, it was not until the 1990s that molecular tools became available to more readily define the genetic basis for such differences. At the turn of the 21st century, advances in genomic technologies created the opportunity to study multiple genes, and pharmacogenomics came into vogue. Distinct definitions for pharmacogenetics and pharmacogenomics can be argued, but these terms are often treated as synonyms. I use the

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Additional information

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term *pharmacogenetics* because, in the clinical setting, attention is typically focused on one or two genes to guide a specific clinical decision.

In the late 1990s and early 2000s, pharmacogenetic research accelerated rapidly. After the completion of the Human Genome Project in 2003,[2] there were many proclamations that genetically guided drug therapy would be commonplace shortly thereafter. In 2004, the American College of Clinical Pharmacy published *Pharmacogenomics: Applications to Patient Care* in an attempt to educate and provide pharmacists with the requisite knowledge to be clinical leaders as pharmacogenetics moved into the clinical arena.[3] It was primarily the lay media and not the scientists working in the field who projected such rapid movement of these approaches into clinical care, but progress was slower than projected. Many people, including numerous pharmacists, began to dismiss the idea that pharmacogenetics would ever have clinical value.

Some of those pharmacists turned into naysayers, but they now risk being left behind in an important opportunity for the profession of pharmacy. Precision approaches to care are increasingly common and becoming the norm in cancer care. President Obama announced in his 2015 State of the Union Address the intention to invest significant resources into advancing the use of genomic and other personal information to improve the prediction, prevention, and treatment of disease.[4] The Precision Medicine Initiative is now moving forward, and initial funding by the National Institutes of Health (NIH) to support the Precision Medicine Initiative has been awarded. Of the 5700 articles related to precision medicine that were published between January 2015 and July 2016, many focused on implementing precision medicine approaches into clinical care. Pharmacogenetics is just one element of precision medicine but is a key approach to precision drug therapy. Even before the focus drawn to precision medicine by President Obama, many institutions had begun implementing pharmacogenetics into clinical care.

The best news for pharmacists and pharmacy is that in many of the institutions implementing pharmacogenetics, pharmacists (including those in academia, pharmacists practicing at an academic medical center, and many in the private sector are playing major leadership roles in the effort, not only as clinicians at the patient interface but also by helping to define what pharmacogenetic testing will be implemented into clinical practice and for which drugs, building the informatics tools, and providing education to pharmacists, physicians, and nurses, among other roles, as previously described.[5] These roles are highlighted in several of the articles in this issue of *AJHP*, along with the medical literature.[5–11] Additional evidence of the leadership of pharmacists in this field is the Clinical Pharmacogenetics Implementation Consortium (CPIC), which provides evidence-driven guidelines that describe how and when to use pharmacogenetic data when they are available.[12] A high percentage of the CPIC guidelines list pharmacists as first or senior authors,[13] and the majority of participants in the pharmacogenetics interest group of NIH's genomic medicine implementation network, Implementing Genomics in Practice, are pharmacists.[14] Clearly, pharmacists are stepping forward in significant ways to help advance the use of pharmacogenetics as a clinical tool.

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But at the same time, it is my observation that there are some pharmacists who either pay no attention to this area of practice or profess that while pharmacogenetics has led to some interesting research, there is little chance it will be of clinical value. These pharmacists are choosing not to advance their knowledge in the area, not to adhere to their paradigm of lifelong learning, and, in a few cases, to work to actively obstruct such change.

A common refrain is that no randomized controlled trials (RCTs) have demonstrated that the use of pharmacogenetic data clinically improves outcomes. While this is largely true, to my knowledge there are no RCTs documenting that adjusting drug doses based on renal function or adjusting therapy to avoid drug interactions leads to improved patient outcomes. Further, the number of RCTs documenting the clinical benefit of therapeutic drug monitoring is limited. Yet pharmacists would largely argue that such trials are not needed, that if we know the renal clearance of a drug, that accumulation of the drug in renal impairment occurs, and that there is some relationship between drug concentration and toxicity, it is only logical that dosing should be adjusted based on renal function. The same logic applies to drug–drug interactions, as the drugs are tested together to define the impact of the interaction but RCTs are never conducted to prove that avoiding the drug interaction leads to better outcomes. Instead, we simply seek to avoid the drug interaction.

Why are the pharmacogenetic examples held to a different standard when most of the clinically actionable scenarios to date (outside of cancer therapies targeted at specific tumor genetics) center around drug metabolism and pharmacokinetic differences, the same drivers of dosing adjustment in renal impairment, drug interactions, and therapeutic drug monitoring? If we can predict that a prodrug will not achieve sufficient concentrations to be effective or that a parent compound will have elevated concentrations that may increase toxicity based on genetic variation, why would we not want to use this tool? In addition, a genetic test for germline variation (i.e., inherited, not somatic or tumor genetics) needs to be conducted once in a patient's lifetime, whereas tests for renal function and therapeutic drug monitoring are performed repeatedly over time.

Pharmacists should not get caught up in what has been called "genetic exceptionalism," the idea that genetics is something very different from other clinical tools and therefore must be held to a different standard for use in clinical care.[15,16] As described above, pharmacogenetics simply presents an additional tool to be used for individualizing care. The patient care goals for pharmacogenetics, namely improving the patient's response to therapy and avoiding adverse drug reactions, are consistent with typical healthcare priorities and quality metrics.

In considering the role of pharmacogenetics in healthcare, we should also consider that the naysayers may be wrong. What if pharmacogenetics represents an important tool that can improve the lives of our patients? My colleagues and I recently presented at the American Heart Association Scientific Sessions the outcomes data on our clinical implementation of *CYP2C19* genotype testing to guide antiplatelet therapy after percutaneous coronary intervention (PCI).[17] Clopidogrel is a pro-drug, and individuals who carry loss-of-function genetic polymorphisms for *CYP2C19* have reduced generation of the active metabolite and reduced antiplatelet activity.[18–20] Numerous retrospective genetic analyses of large RCTs

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suggest that patients undergoing PCI with a loss-of-function allele have worse outcomes when treated with clopidogrel.[21] Yet the cardiology community has largely dismissed genotype-guided antiplatelet therapy on the basis that there are no clinical trials documenting the benefit of such an approach.[22] But what if the community is wrong? What if patients with *CYP2C19* loss-of-function alleles should be treated with another drug? The risk in this scenario is that if the patient continues taking clopidogrel, a cardiovascular event may occur due to an insufficient antiplatelet effect from clopidogrel. Alternatively, what is the risk of the pharmacogenetic approach? In this case, the risk is that the patient may be placed on a different, highly effective antiplatelet agent that is more expensive. Our data suggested that patients with a *CYP2C19* loss-of-function allele who continued to take clopidogrel had significantly higher rates of major adverse cardiovascular outcomes (death, myocardial infarction, stent thrombosis, stroke) than those who were switched to an alternative drug.[16] This is fully consistent with what we know about the impact of the genetic polymorphism on active drug concentrations, the antiplatelet effect, and what the retrospective analyses of the RCTs suggest. Does it really make sense to adopt the “no RCT” mantra and assume the potential risk when there is a safe and effective alternative? There are, of course, examples that are not so straightforward, where there may not be a good alternative or the alternative is suboptimal, as may be the case for genetic variants of *CYP2D6* and their effect on the metabolism of tamoxifen, where acceptable alternatives may be limited for women with premenopausal breast cancer.[23] In those cases, a more careful approach is warranted. But most of the examples covered in the CPIC guidelines are like the examples of *CYP2C19* and clopidogrel, not like *CYP2D6* and tamoxifen.

Economic factors also pose certain barriers to the use of pharmacogenetic testing, as there is variability in the reimbursement for pharmacogenetic tests. Many who are implementing pharmacogenetics in the clinical setting believe that a panel-based test—one that tests for multiple genes at once for use over a patient’s lifespan—is the most cost-effective and logical approach to implement pharmacogenetics.[24] However, the Centers for Medicare and Medicaid Services, and therefore most other payers, currently have provisions that prohibit reimbursement for panel-based tests. These economic challenges are common across various types of genetic testing, not just for pharmacogenetics. Therefore, efforts are underway to build an evidence base for the economic benefits of a pharmacogenetics-guided approach to drug therapy, and many are working actively with payers to understand the evidence they seek to move pharmacogenetics into the mainstream of care.

The current reality is that the pharmacogenetics train is gaining steam and starting to pull out of the station. Numerous pharmacists are creating the energy and momentum for that forward movement, but much broader and deeper participation from pharmacists is required for pharmacogenetics to have its greatest impact. Pharmacists should be knowledgeable about pharmacogenetics and the settings where its use has clinical value and learn about the approaches for facilitating its implementation into care. They should be change agents and jump on the train.

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