

## A Valuable Insight Impact of Pharmacist in Pharmacogenomics

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### Review Article

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**Abstract:** Pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, decrease the chance for adverse drug events and increase the effectiveness of drugs. Pharmacist must be aware with the new technologies so as to take advantage of these new opportunities for the benefit of patients. Pharmacist must further develop a process to effectively deliver pharmacogenomics services to individual patients that are aligned with medication therapy management (MTM) service delivery, develop a viable business model for these practices and encourage the development of health information technology solutions that support the pharmacist's role in this emerging field. The purpose of article is to highlight the recent development in pharmacogenetics in which pharmacists may play a vital role in the context of pharmacogenetics study approaches and factors to consider when applying pharmacogenetics discoveries to patient care.

**Keywords:** Pharmacogenomics, Pharmacogenetics, Pharmacist, MTM, TDM and NCHPEG.

### INTRODUCTION

Pharmacogenetics is defined as the study of inherited variation in drug-metabolizing enzymes and drugs responses. The term has been used interchangeably with Pharmacogenomics, which is defined as the overall study of how genes affect drug behavior and not focused solely on drug metabolizing enzymes and response [1,2].

The aim of pharmacogenetics is to shape therapy with available medicines in individualized fashion. The future of pharmacogenetics needs a strong implementation in pharmacy practice. The success in clinical application of pharmacogenomics technologies and information will be effective collaboration among the health disciplines, advances in pharmacogenomics research also will benefit from a broad inter professional and multidisciplinary research agenda that includes scientists, physicians, pharmacists, nurses, genetic counsellors, payers, and other stakeholders [3-5]. Moreover the various genes and their isoforms that play important role in individual's variations in drug response by modulating diverse physiological pathways have been identified as shown in Figure 1.

Pharmacists as educators, clinical consultants and providers of health care will likely influence the way that pharmacogenomics information is used in medical practice and contribute in unique and vital ways [6-8]. Currently, pharmacists perform a variety of roles in the health care setting, including educating patients and providers, selecting and monitoring drug

therapies for individual patients, ensuring safe and appropriate use of medications in populations, and conducting clinical research. The pharmacogenetics revolution will provide unique opportunities for pharmacists to expand these roles as personalized medicine evolves [9-11].

In contrast, the term 'genetics' relates etymologically to the presence of individual properties as a consequence of having inherited them. The term 'pharmacogenetics' is sometimes used in a restrictive sense to describe how different gene variants affect drug-response but it can also be defined more broadly as the study of the effect of heredity on human drug-response. With recent developments in genome mapping, it has become possible to study pharmacogenetics on a genome-wide basis and the term 'Pharmacogenomics' has been coined to describe this new field. Studies assessing the impact of different genotypes on drug response may lead to novel insights into biochemical disease pathways, and hence to identification of potential molecular markers

(biomarkers) useful for disease monitoring during therapy [12-14].

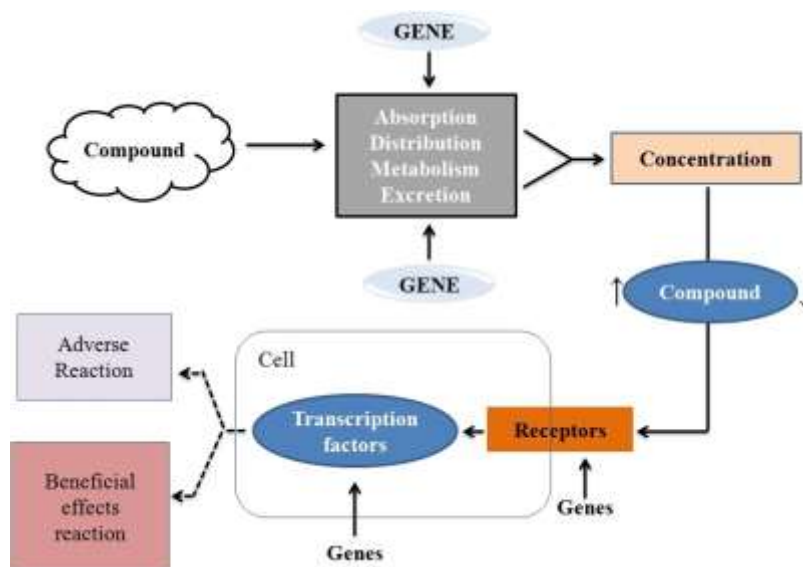


Figure 1: Diagrammatic representation of mechanisms involved in altered response to a compound and its possible pharmacogenetics targets.

Complex and multifactorial cause of variations in drug response have been suggested among them the genetic factor are the most important which may be due to variation in therapeutic targets, drug metabolizing enzymes, drug transporters, targets of adverse drug reaction and factors with indirect effect [12, 14-16]. The differences in drug response due to individuals' genetic variation can be discussed under two broad headings; Drug do not work in some individuals and drugs

produce severe adverse drug reactions at clinical relevant therapeutic dose. In the first case, there is sufficiently reduced response to some medication such as antipsychotics, COX-2 inhibitors, antidepressants, antiasthmatics, drugs for Alzheimer's disease and chemotherapeutic agents in some treatment groups. However, in second condition some individuals experience severe adverse drug reaction with the normal therapeutic dose (Figure 2).

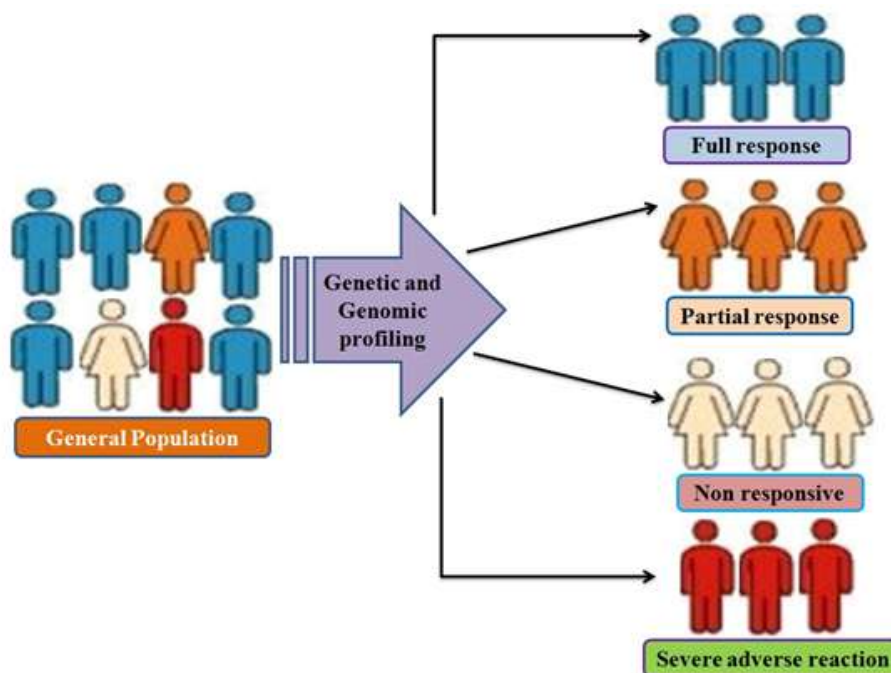


Figure 2: Hypothetical representation of population and responders of drugs based on pharmacogenetics.

There is limited knowledge about pharmacists' opinions regarding pharmacogenomics and their impact on the profession or pharmacists' self-perceived confidence in the practical application of pharmacogenomics information in the scientific literature. Thus, this article provides an insight on current thinking and application of pharmacogenetics concepts and possible role of pharmacists. Here we discussed in brief the different facets of pharmacogenetics and then thereafter we discuss the impact of pharmacogenetics on clinical pharmacy [17-19].

### Challenges and Role of Pharmacist

The changing face of healthcare also includes changes for pharmacists. With focus on the greater utilization of their skills, the role of pharmacists is moving away from remuneration for dispensing medicines towards being rewarded for providing an extended range of services. The roles that pharmacists play in pharmacogenetics have not been clearly defined, and little is known about the future roles of pharmacists in the field. However as practitioners whose training and practice focuses on the clinical monitoring of drug treatment, pharmacists are in a valuable position to help in defining the eventual role of pharmacogenetics in pharmacotherapy [20-22].

### Establishment of Pharmacogenetics Testing in Clinical Practice

Translation of research is an important step in the implementation of early research findings in patient care. Pharmacists have a role in the early steps of pharmacogenetics research and in testing the application of early research results in patient care settings. Once a relationship between drug response and genetic variation has been established, subsequent research should establish the use of pharmacogenomics testing as measured by specific therapeutic outcomes. Pharmacists can help develop ways to evaluate the application of testing in patients, with the goal of proving or disproving that pharmacogenomics testing adds benefit to clinical practice. Pharmacogenomics models would be most useful in complex drug therapies that require individualized dose management, such as epileptic, lipid, anticoagulation cardiovascular, and hypertensive management. Consequently, because of the complex drug therapy and management of these conditions, pharmacists already tend to be involved in these areas and, in some cases, are managing medication therapies under collaborative agreements [22-25].

For example: Warfarin, is an anticoagulation medication that has a narrow therapeutic window. Bleeding, the most common adverse effect of warfarin, occurs in 6% to 39% of treated patients each year and is most common at initiation of therapy [26,27]. Early studies showed that warfarin was metabolized by

cytochrome P450 (CYP) enzymes, particularly CYP2C9. Subsequently, the gene encoding CYP2C9 was found to have many variant alleles that were differentially expressed in various populations. Expression of these variant alleles, particularly CYP2C9\*2 and CYP2C9\*3, were shown to affect the metabolism rate of various drugs such as warfarin. Approximately 8% to 20% of whites are carriers of the CYP2C9\*2 allele and 6% to 10% are carriers of the CYP2C9\*3 allele [28]. Asians and blacks have lower frequencies of these variant alleles [28,29]. When compared with patients who were homozygous for the wild-type (CYP2C9\*1) allele, patients with one copy of the CYP2C9\*2 allele required warfarin maintenance doses that were 20% lower and patients with one copy of the CYP2C9\*3 allele required warfarin doses that were 34% lower [29,30]. An even more dramatic decrease in dose was required for those who were homozygous or heterozygous for the CYP2C9\*2 and/or CYP2C9\*3 alleles, which would require a 60% to 75% dose reduction [26,31]. Furthermore, those with variant alleles were found to have a significantly increased risk of developing serious bleeding events [31].

Once prospective studies have been established the clinical relevance of genetic testing and the regulatory, ethical, and economic aspects of such testing need to be considered. From a regulatory standpoint, FDA has partnered with industry to establish workshops and advisory groups that discuss and develop policies related to pharmacogenetics [32]. FDA encourages voluntary submission of genomic data during the drug development process. In addition, the agency recommends including pharmacogenetics information in the package insert if the data affect the safety and efficacy of a particular drug [18]. Several drugs have been investigated in detail for associations between enzyme polymorphisms and drug toxicities and/or therapeutic benefit. For some, the evidence for genotype-associated toxicity or efficacy is substantial enough that information on pharmacogenetics testing appears in the drug label. To this end, pharmacists should be aware of the regulatory issues surrounding these medications and the implications of the label information for clinical practice.

Chemotherapeutic agents have been researched extensively. These agents are especially challenging to administer because of their narrow therapeutic windows and interpatient variability in how the agents are metabolized and cleared from the body. Currently, initial doses of chemotherapeutic agents are based on body weight or surface area, with dose adjustments made after signs of toxicity appear. Pharmacogenetics testing aims to associate specific genetic polymorphisms with clinical outcomes in patients treated with commonly prescribed chemotherapy drugs, thereby predicting the toxicity and/or efficacy of a

particular dose of a particular agent for an individual. The toxicities of some medications have long been known to be associated with genetic variations [33-35].

Another example is thiopurine S-methyltransferase (TPMT) and the antimetabolite mercaptopurine (Purinethol-DSM Pharmaceuticals). Similar to irinotecan, mercaptopurine is a chemotherapeutic agent that has been rigorously studied for associations between genotype and toxicities and/or efficacy [33,36]. Mercaptopurine is used in the treatment of acute lymphoblastic leukemia. TPMT is a polymorphic enzyme that converts mercaptopurine to its inactive metabolite. Thus, patients who are TPMT deficient are at high risk for myelosuppression and secondary tumors with administration of mercaptopurine or other thiopurines (e.g., azathioprine) that are converted to mercaptopurine. Conversely, patients with high TPMT activity may experience a decreased therapeutic effect from treatment with these agents. Approximately 0.3% of whites and blacks have two non-functional alleles of the TPMT gene leading to little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele and have low or intermediate TPMT activity [21,33,34,36]. Further, it has been recognized that pharmacists play an important role in implementation of pharmacogenetics services in clinical setting by their services at the point of prescription, at the point of dispensing and integration of new pharmacogenetics services. This section will be structured around three themes.

#### **Pharmacogenetics at the Point of Prescription**

At present, pharmacogenetics at the point of prescribing is likely to involve only a small number of pharmacists in highly specialized roles, such as in oncology pharmacy, although this is likely to change in the future, permeating through into the primary-care setting. The persons most likely to order a test at this point in the care pathway are the prescribers themselves, using the information obtained to inform drug choice and dosage. As pharmacists increasingly take on prescribing roles, this aspect of pharmacogenetics is likely to increase in importance and relevance [1,2,3,5,8].

#### **Pharmacogenetics at the Point of Dispensing**

Hospital pharmacists may play a greater role in the application of some of these emerging therapies, but this is unlikely to have a major impact on demand. Within the current practice framework, pharmacogenetics advice, based on information from various sources, notably the drug data sheets, can be given by the pharmacist at the point of dispensing and sale. The advisory role of the pharmacist, which includes informing patients about how to take their medications and how to avoid drug-drug and drug-diet interactions, is simply expanded to include

pharmacogenetics without structural alteration in practice pathways [20,21,37,38].

#### **Integration of Pharmacogenetics Services**

This aspect will require alteration in clinical practice but will build on the expanded services, which are being developed or piloted by pharmacists with the support of the Department of Health. Examples include the provision of testing for Chlamydia, diabetes and blood pressure monitoring, and medicines management services. Drug monitoring, such as of warfarin, with blood coagulation testing (prothrombin INR measurement) which takes account of cytochrome P450 2C9 and VKORC1 genotypes polymorphism may well form part of this service. The extent to which pharmacists are involved in the actual genotyping had yet to be defined. They could act as intermediary in the collection and dispatch of samples, or simply as interpreters of test results. Private consultation rooms that are being established in many pharmacies would be essential for this expanded service [29,31,38].

The differences in the application of pharmacogenetics in primary, secondary and tertiary care arose during the discussion. It was felt that in secondary care, pharmacists were more likely to have protocols to follow and to have more information available to them. However, as patients have fewer follow-ups in the secondary-care setting, pharmacogenetics issues will increasingly impact on the work of the general practitioner and community pharmacist. A distinction was also made between the roles of pharmacists who work in a generalist setting and those who work in a specialist clinical area, such as oncology. It was suggested that generalists would need to appreciate that pharmacogenetics existed, what the 'red flags' were and when they should refer a patient on to a specialist. They should also be able to answer patients' questions and know where to obtain more information. Specialist practitioners would require more detailed information on how pharmacogenetics impacted specifically on their practice [39,40,41]. Some specialty areas in pharmacy profession have been recognized where pharmacist play important role such as:

#### **Pharmacogenetics with Community Pharmacy**

Some participants from the community pharmacy setting voiced the opinion that there would need to be drivers to integrate pharmacogenetics into practice, both in terms of clinical evidence and financial incentives. It was also felt that the education and information for community pharmacists would need to be at a very practical level; i.e. this drug should not be prescribed unless this test has been carried out [13,40,41].

#### **Pharmacogenetics with Oncology Pharmacy**

Within the oncology setting, pharmacogenetics is a part of existing pharmacy practice and may well be the area where uptake of pharmacogenetics will be greatest in the short-term. Experience gained in this setting should be collated and disseminated to other clinical areas to aid the integration of pharmacogenetics as it becomes clinically appropriate. In cancer treatment, genetic testing can pinpoint patients who will benefit from certain drug therapies. For a woman with breast cancer, a diagnostic test can determine her tumor's genetic signature. If the patient tests positive for human epidermal growth factor receptor 2 (HER-2), she can be given trastuzumab, which suppresses excess HER-2 and thereby 50% reduction in the recurrence risk of disease [10,33,36].

### **Pharmacogenetics with Drug Development and Regulation**

Participants believed that as pharmacogenetics becomes embedded into the drug development process this would lead to the development of genetic tests to accompany an increasing number of new drugs. Pharmacists working in drug-regulatory bodies and the Department of Health have an important role to play in facilitating an evaluation system and championing the uptake of drug-test combinations that fulfill the relevant clinical and economic criteria. This section will give further consideration to the nature of the tasks that this role would require and the skills that pharmacists would need to fulfil the role. It has been agreed upon during the meeting from the NHS National Genetics Education and Development Centre that there is need to carry out an exercise with participants to identify the skills required by pharmacists in order to integrate pharmacogenetics into their practice [32,42,43].

According to the themed groups assembled by participants, to be able to integrate pharmacogenetics into practice, a pharmacist should be able to; critically appraise evidence, make decisions, manage risk and prescribe, Acquire relevant knowledge, understand one's own limits, refer and work as part of a team, Obtain, handle and test patient samples, Interpret test results, Solve problems and keep appropriate records, Develop diagnostic and disease monitoring skills, synthesize patient data and genetic data, Communicate effectively and Provide relevant counselling, obtain informed consent and communicate test results and their wider implications [40,41,42].

For each of the activities that participants identified, they were asked to indicate whether they believed that this should be applicable to pharmacists working in a generalist role, specialist pharmacists, or both. In the majority of cases, it was felt that the skills were relevant to pharmacists in both roles. The exception to this surrounded the testing process itself. Participants suggested that that whilst taking samples from patients could be done by both generalist and

specialist pharmacists, interpreting test results and making recommendations from these results should be done by specialists only. There was also a lack of agreement about whether generalist pharmacists had a role to play in interpreting pharmacogenetics test results [39,40,41].

The skills highlighted were generic, almost all of which pharmacists already had and used on a regular basis. This suggested that the implementation of pharmacogenetics on a wider-scale would not require pharmacists to acquire new skills. Instead, they would need to apply these existing skills to newly acquired knowledge within the context of a pharmacogenetics service and decide who does what within existing roles.

### **Developments of Research Methodologies and Projects**

The pharmacogenetics roles that pharmacists can play in this regard will likely be patient centered and focused on optimizing disease and health-related quality-of-life outcomes [4]. However, pharmacists are also in a unique position to drive the early stages of clinical and translational pharmacogenetics research through their understanding of pharmacokinetics, pharmacodynamics, and the relevant clinical and economic systems that drive health care delivery as either principal investigators or key members of a research team [3]. Within both academia and the pharmaceutical industry, pharmacists have been involved in the early stages of pharmacogenomics research for specific diseases in which drug therapy is an important management component. As might be expected, this has begun with a focus on drug therapies that are inconsistently effective (i.e., large heterogeneity in clinical response) and prone to adverse effects [41,42,43].

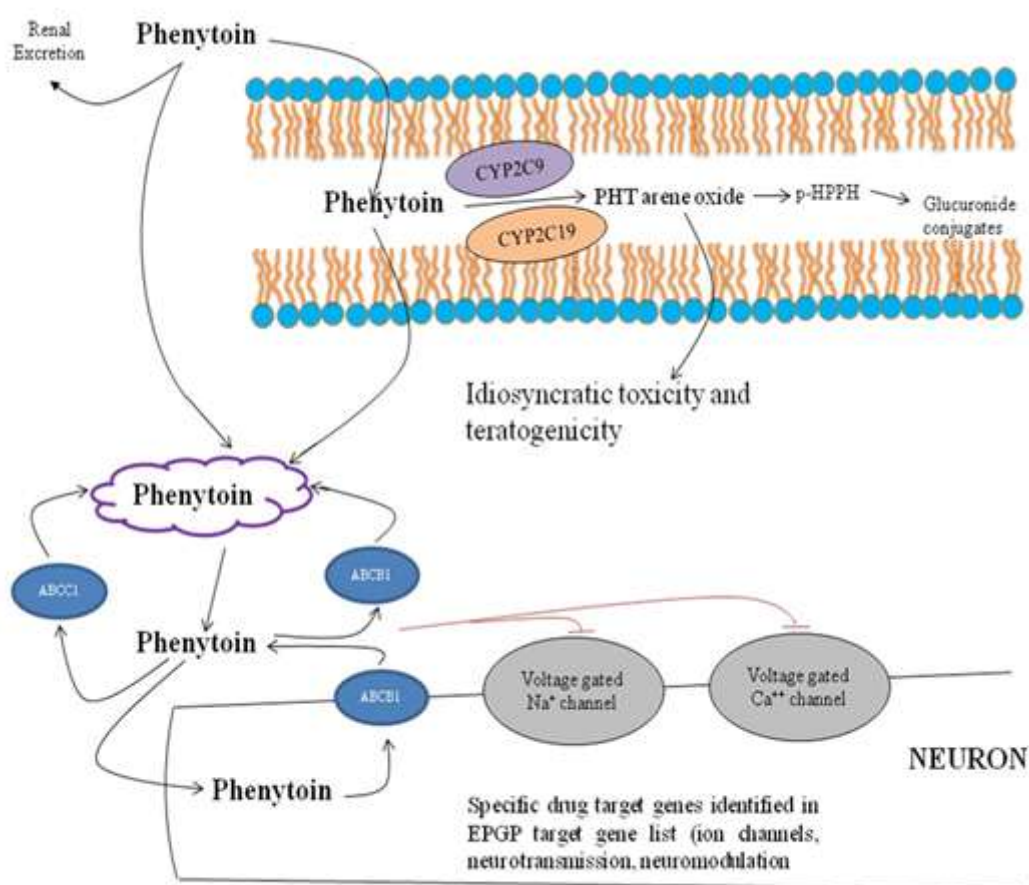
Although variation in a single gene can have a profound influence on drug response (e.g., effect of thiopurine methyltransferase polymorphisms on azathioprine-induced myelosuppression), most drug responses are thought to be complex, involving multiple genes that interact as part of a drug response "pathway." As such, delineating drug response pathways by representing the various genes involved in drug responses has been a useful tool in the early phases of pharmacogenomics research for selected drugs and diseases. Polymorphisms in any of the genes shown in this pathway could have an influence on clinical response to phenytoin. One limitation to this approach is that our understanding of all the relevant components (genes and proteins) of a drug pathway is limited. However, because pharmacists are highly knowledgeable regarding the various pharmacokinetic and pharmacodynamics components that are likely involved in clinical drug response (e.g., metabolizing enzymes, transporters, drug targets), they should be viewed as valued allies in the construction of

comprehensive pathways for better treatment outcomes [39,41].

For example, the role of pharmacist developed in large part as a result of the pharmacokinetic complexity of standard antiepileptic drugs. The inconsistent effectiveness of these agents, there is perceived need for educating patients regarding the desired and undesired effects of antiepileptic drug therapy, and the need for frequent medication revisions in the predominantly pharmaco-resistant patient population that was referred to this specialty centre.

Preliminary evidence suggested associations between genetic variance and epilepsy susceptibility (particularly for rare Mendelian types of epilepsy) and

antiepileptic drug metabolism, but the contribution of genetics to common epilepsy types and clinically relevant drug response phenotypes had not been adequately studied [17]. A group of investigators in collaboration with epileptologists and a pharmacogenetic scientist, the pharmacist developed the rationale for including pharmacogenetics as an important component of this large study, for which grant support was requested from the National Institute for Neurological Disorders and Stroke (NINDS). This group of four, comprising the pharmacogenetics core of the project, collaboratively developed drug response pathways for relevant antiseizure drugs (Figure 3) and the detailed phenotyping instrument for pharmacoresponse.



**Figure 3:** Pharmacogenetics mechanism of antiseizure drug (Phenytoin) associated altered response and their possible targets.

As the example above illustrates, pharmacists have expertise in areas that are highly relevant to the early stages of pharmacogenomics research. They have an appreciation for many of the factors that drive the expansion of pharmacogenetics into new areas of disease management, such as knowledge of drug treatments (e.g., anticancer and antiseizure drugs) for which efficacy and responses are unpredictable, drugs that cause serious adverse events (e.g., antipsychotic

medications and hepatotoxins) and, serious and nonserious adverse drug events or complications that cause drug failure or substantially delay successful treatment of disease (e.g., need for frequent dosing adjustments of warfarin resulting in delays to therapeutic anticoagulation). Drug treatments that have marked efficacy in small subpopulations but dramatically less efficacy in the larger population of

patients with a given disease (e.g., gefitinib response in patients with non-small-cell lung cancer) [9,17, 32].

### Pharmacists as Key Factor in the Healthcare Sector

Pharmacists are key actors in the healthcare system and a central part of the patient experience of health and illness. Over the past 40 years, there has been great progress toward integrating pharmacists as members of the healthcare delivery team as well as in shifting daily activities from dispensing medications to delivering personalized pharmacotherapy services [21,37,38,40,43]. With the recent extensions to their professional role into more clinical work activities pharmacy practice has been re-located away from the dispensary onto the shop floor (in the case of community pharmacy) and to the patient bedside (in the case of hospital pharmacy). This has generated new ways in which pharmacists interact with medicines and patients. Despite this, there has been relatively limited sociological attention given to pharmacy practice, particularly in the pharmacogenetics study settings. While the pharmacy profession has fostered development of the clinical pharmacist, laboratory-based researchers have been discovering underlying pharmacogenomics principles and relationships, bringing the 2 concepts closer to a complementary relationship rather than a mutually exclusive one [2]. In 2007, the national Coalition for Health Professional Education in Genetics (NCHPEG) published core competencies for all healthcare professionals designed to serve as a framework for continuing healthcare education. Hopefully, these competencies, which involve knowledge, skills, and attitudes, will result in healthcare practitioners integrating genomics into their daily practice. (<http://www.nchpeg.org/index.php>).

While it would seem intuitive for the practice of clinical pharmacy to encompass pharmacogenomics, the results of the current study clearly demonstrate that pharmacists lack self-confidence in their ability to base therapeutic decisions on pharmacogenomics. These results are corroborated by an evaluation in the community pharmacy setting in which pharmacists rated themselves as less than 40% (scale of 0% to 100%) confident in their own knowledge of the human genome project, pharmacogenomics, and genetic testing [41].

Practitioners also have demonstrated a lack of confidence in clinical collaborative practice, another rapidly expanding area of pharmacy. One survey found that less than 50% of community pharmacists had adequate confidence in their clinical knowledge or felt sufficiently trained to provide clinical services to general practitioners. Despite these findings, the longitudinal portion of the survey found a 16% increase in general practitioners' confidence that their local pharmacists are capable of providing medication management services in 2002, compared with results

from 1998 [13]. While efforts underway to improve the pharmacogenomics knowledge base of new Pharm D graduates represent progress, it is equally essential that practicing pharmacists receive continuing education in pharmacogenomics. As the results of the current survey indicate, continuing education emphasizing the importance of pharmacogenomics in the profession of pharmacy may be necessary to ensure that seasoned practitioners recognize the significance of this science. In 2001, an assessment of pharmacogenomics continuing education at 3 national pharmacy meetings found over 60 hours of educational offerings devoted to the topic. Pharmacists attending these meetings could easily spend almost half (45%) of their time on pharmacogenomics sessions alone [4,6]. Despite the available continuing education, this study and another conducted in the community pharmacy setting indicate a lack of association between the availability of continuing education and its impact on pharmacists.

There is growing evidence for the clinical utility of pharmacogenetics, and pharmacists can play an essential role in the thoughtful application of pharmacogenetics to patient care. Moreover, the role of pharmacist in therapeutic drug monitoring (TDM) is well accepted by the healthcare professionals. In addition to this, it has been agreed upon that there must be a design and implementation of pharmacist-managed clinical Pharmacogenetics service to improve the treatment outcomes. The service is modelled after integration with pharmacist working in already established Clinical Pharmacokinetics centre. All clinical pharmacogenetics test results need to be first reported to one of the pharmacists, who review the result and provides a written consult. The consult includes an interpretation of the result and recommendations for any indicated changes to therapy [19,20,39,42,43].

Finally, compared with pharmacists in other settings, pharmacists in this type of environment may discuss or order Pharmacogenomics tests more often, thereby incorporating Pharmacogenomics into their daily medical and pharmacy practice. While this factor did not translate into substantial pharmacist confidence in our study, the confidence of pharmacists in other settings may be different. However, because the current survey included pharmacists at a large teaching hospital as well as those in outlying community medical centers, the results may be generalizable to a variety of institutions and pharmacists.

### CONCLUSION

Pharmacogenetics may not be a part of routine clinical and community practice for some time; therefore, the field presents opportunities for a wide range of pharmacists, from the basic scientist to the clinician to the administrator, to collaborate with other health professionals in pharmacogenetics discovery and

application. Pharmacists are already engaging in some of these roles and paving the way for future pharmacist involvement in personalized medicine and pharmacogenomics research. The case examples reported here offer insight into future roles for pharmacists in pharmacogenetics. At some point, all pharmacists, not just those involved in a clinical or research setting, will probably need to understand pharmacogenetics information to better aid in drug selection.

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