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Pharmacogenomics: Your Medical Identity

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Abstract
Pharmacogenomics, the fusion of pharmacology and genomics, shows strong potential to solve many of today's dosing problems. Inter-patient dosing requirements, mainly due to genetic variability between patients, represent significant challenges for prescribers. Certain receptors, drug-targeted proteins, drug transport mechanisms, and drug-metabolizing enzymes are genetically established. Hence, any defect, absence or abnormality in the gene could alter how an affected individual will respond to a given drug. Due to advancements in technology, health care professionals who utilize pharmacogenomics may assess a patient's genetic profile and determine a predicted response to specific medications. This may result in potentially optimal dosing at the onset of treatment rather than going through a trial-and-error process that could take many months. Despite the recent developments in pharmacogenomics, several barriers must be crossed before the benefits of personalized medicine can be fully appreciated and widespread. Some of these barriers involve limited knowledge, testing, and heated ethical debates. This article provides an overview of pharmacogenomics for the pharmacist.

Introduction
One size fits all. In drug therapy, this is rarely true but, unfortunately, it is often the approach used when treating patients. If the initial dose is suboptimal, then the dose is adjusted. For example, clopidogrel is an oral antiplatelet drug that is typically initiated at a dose of 75mg once daily. The effectiveness of this drug depends on its activation to a reactive metabolite by the cytochrome P450 (CYP) system. Patients who are "poor metabolizers" may experience a thromboembolic event due to sub-therapeutic levels of active drug before the drug is appropriately dosed. Conversely, patients who are rapid metabolizers of clopidogrel may have increased levels of active drug and experience adverse bleeding events. This trial-and-error dosing tandem will likely continue until the optimal therapy is achieved or alternate treatment is prescribed. This delay in appropriate treatment may result in undesirable consequences for the patient and increased health care costs. What if there was a way to stop this cycle and effectively treat the patient the first time?

New technological advances have the potential to aid health care providers in selection of appropriate drugs and dosage regimens personalized for individual patients. In addition, this new technology may predict patients likely to experience adverse drug reactions. With adverse drug reactions ranked high in the top causes of preventable death, personalized medicine may decrease the number of occurrences and save lives. This concept of individualized drug therapy may be realized with the use of pharmacogenomics. In fact, the FDA endorses the application of this field as evidenced with a recent change to the product labeling for the above-mentioned drug, clopidogrel. It now contains a black box warning (Figure 1).

The Basics of Pharmacogenomics
Pharmacogenomics is the fusion of pharmacology and genomics. Pharmacogenomics refers to the general study of all of the many different genes that determine drug behavior. Pharmacogenomics refers to the study of inherited differences (variation) in drug metabolism and response. Although these two disciplines are different, the distinction between them is considered arbitrary by many researchers. Currently, it is not unusual for the two terms to be used interchangeably.

Certain receptors, drug targeted proteins, drug transport mechanisms and drug metabolizing enzymes are based on a person's genetic code; thus, it can be concluded that any defect, absence or abnormality in the gene has the potential to alter how an affected individual will respond to certain drugs. The genes most commonly studied are those that code for enzymes that metabolize drugs; these enzymes affect the drug's pharmacokinetic and pharmacodynamic properties.

The alteration of the gene is typically the result of a single nucleotide polymorphism (SNP). SNPs are DNA sequence variations that occur when a single nucleotide base in the gene sequence is altered. A SNP within a gene has the potential to cause a missense, sense or nonsense polymorphism in the protein it codes for. A missense polymorphism results in a code for a different amino acid than the unaltered gene. A sense polymorphism results in the same amino acid as intended, but by a different sequence. A nonsense polymorphism results in the early termination of the protein synthesis. SNPs are among the top genetic variations being examined today because a single SNP within a gene can alter protein expression of such enzymes as cytochrome P450 (CYP) metabolizing enzymes.

Clinicians take advantage of a patient's genetic profile to fit their specific needs at the onset of treatment rather than go through a trial-and-error process that can take many months. Not only does this save time and money, but pharmacogenomics can also prevent many adverse drug reactions. Adverse drug reactions are among the leading causes of death in the United States. Many drugs can elicit an adverse reaction in some patients and not in others. Consequently, it is important to screen a patient's genetic profile before selecting a potentially dangerous medication. The utilization of pharmacogenomics has the potential to significantly lower the incidence of adverse reactions.

Pharmacogenomics: Past
The first use of pharmacogenomic technology was in 1932 when the ability to taste phenylthiocarbamide was tested and evaluated. Pharmacogenomics: Your Medical Identity

Figure 1: Plavix® (clopidogrel) Black Box Warning
Adapted from products.sanofi-aventis.us/plavix/plavix.html

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Effectiveness of Plavix® depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19
- Poor metabolizers treated with Plavix® at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy

Figure 1: Plavix® (clopidogrel) Black Box Warning
Adapted from products.sanofi-aventis.us/plavix/plavix.html
It had been observed that some populations had the ability to taste the compound, while others did not. Those identified as being unable to taste the chemical compound were autosomal recessive (did not code) for the enzyme that enabled them to taste the compound. Through this study, researchers concluded that genetic makeup determined how an individual would respond to certain chemicals or drugs.

During the 1940s and 1950s, scientists began investigating the mechanisms and impact of cytochrome P450 on the metabolism of drugs. It came to the attention of some scientists when they noticed that some patients taking the antihypertensive medication debrisoquine had an enormous decrease in blood pressure. Through further studies, it was determined that the specific population experiencing this effect had two recessive alleles coding for the enzyme responsible for metabolizing the medication. The lack of metabolizing enzyme caused an exacerbation of the drug's effects due to an accumulation in the body. The discovery further supported what researchers had hypothesized in the 1930s. The extent to which a drug is metabolized is highly influenced by a person's genetics.

Pharmacogenomics: Today

Currently, the official product labeling in more than 20 medications now mention the availability of tests for genetic variations that impact the drug's action (Table 1). However, testing is optional. The Clinical Trials Web site notes that 365 pharmacogenomic studies are being conducted worldwide.

Table 1: Examples of Current Drugs with Pharmacogenomic Parameters

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pharmacogenomic Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>CYP 2C9</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP 2C19</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Thiopurine methyltransferase</td>
</tr>
<tr>
<td>6-Mercaptopurine (Purinethol®)</td>
<td>Thiopurine methyltransferase</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>5-Fluorouracil (Efudex®)</td>
<td>Dihydropyrimidine dehydrogenase</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
</tr>
</tbody>
</table>

A specific example of how pharmacogenomics can be used today is genetic analysis of CYP2C9 to assist with warfarin dosing. As mentioned previously, SNPs are among the top genetic variations being examined today because a single SNP within a gene can alter protein expression of enzymes such as cytochrome P450 (CYP) metabolizing enzymes. A commonly mutated, clinically significant CYP enzyme is CYP2C9. Instead of initiating a patient on a standard dose, determination of the patient's genetic profile allows the clinician to determine a more appropriate dose from the start. The rationale behind this lies within the CYP2C9 allele. The role of CYP2C9 is to metabolize the S enantiomer to its inactive metabolites. If a patient has a polymorphism within their CYP2C9 allele, they will have an increased risk of bleeding. This is due to a slower metabolism, which allows the drug to stay in the body longer and increases its exposure. Through the use of pharmacogenomics, an adjusted dose can be initiated before the patient even leaves the physician's office, thereby avoiding the extra time waiting for an INR (international normalized ratio) to return and potentially averting a bleed.

A black box warning suggesting pharmacogenomic testing is part of the FDA-required labeling for the antiviral agent abacavir. In this example, patients with a specific allele (HLA-B*5701) are at high risk for experiencing a hypersensitivity reaction. Prior to initiating therapy with abacavir, screening for the allele is recommended. This approach has been found to decrease the risk of hypersensitivity reaction. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir, however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Another enzyme called TPMT (thiopurine methyltransferase) plays an important role in metabolizing thiopurines. A small percentage of Caucasians have genetic variants that prevent them from producing an active form of this protein. As a result, thiopurines elevate to toxic levels in the patient because the inactive form of TPMT is unable to break down the drug. Today, thiopurine methyltransferase genotyping and thiopurine metabolite testing have been established as an adjunct to monitoring patients taking thiopurine drugs such as azathioprine.

Pharmacogenomics: Future

Though pharmacogenomics is considered to be in its infancy, many researchers and health care professionals anticipate significant benefits from its use in the future (Table 2). More individualized medicines will be developed based on the proteins, enzymes, and RNA molecules associated with genes and diseases. Instead of the standard trial-and-error method of matching patients with the right drugs, clinicians will be able to analyze a patient's genetic profile and prescribe optimal drug therapy and dose from the initiation of treatment.

Pharmacogenomics may result in advanced screening for disease, allowing a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Better vaccines, improvements in the drug discovery and approval process, and a decrease in the overall cost of health care are all foreseeable results of pharmacogenomics technology.

Table 2: Future Benefits of Pharmacogenomics

- Optimal drug therapy from the initiation of treatment
- More accurate methods of determining appropriate drug dosages
- Advanced screening for disease
- Vaccines
- Improvements in the drug discovery and approval process
- Decrease in the overall cost of health care

Adapted from: http://www.omim.org/oc TECHNORESOURCES/Human_Genome/medicine/pharma.shtml

Challenges of pharmacogenomics

Despite the recent developments in pharmacogenomics, several barriers must be crossed before the benefits of personalized medicine can be fully appreciated. Due to the frequency of SNPs, millions must be identified and analyzed to determine their involvement in drug response. To further complicate this process, researchers still have limited knowledge of which genes are involved with each drug response. Moreover, several genes are likely to influence drug response, creating an extremely time-consuming and complicated path of study. Although technological advances have led to tests that can identify multiple locations of genes on chromosomes in a short time, the availability of such tests limits their application in patient care. Only a very small percentage of U.S. laboratories offer pharmacogenetic testing, and often they are located...
a considerable distance away from the patient. This results in a lengthy turnaround time for testing outcomes. Furthermore, the cost of pharmacogenetic testing ranges from $250-$500. While testing required by the FDA is usually reimbursed by third-party payers, additional testing beyond what is required by the FDA must be supported by high-quality evidence of clinical value before reimbursement and coverage are considered. Although this evidence may be forthcoming, it is still uncertain if all third-party payers will reimburse for such testing. 

Unfortunately, even if all of the above concerns were overcome, further difficulties may lie ahead. Interpretation of pharmacogenetic tests is particularly important due to their influence on the dosing of drugs. To do this requires knowledge about genetic and non-genetic factors that affect drug disposition and pharmacodynamics. Introduction of these factors into practice will undoubtedly complicate the process of prescribing and dispensing drugs. When only one or two approved drugs are available for a given condition, and genetic variations prevent patients from using them, patients may be left with no alternatives for treatment. Furthermore, drug manufacturers may be unwilling to put forth the time and effort to develop multiple pharmacogenomic products due to the cost of bringing a drug to market. 

Ethical issues in pharmacogenomics

Several concerns exist surrounding ethical issues. The biggest fear for patients related to genetic testing is potential discrimination in health insurance and employment. Some people worry that after undergoing certain genetic testing, information concerning any current health problems, along with health problems that will arise in the future, will not be held completely confidential. Because of this, many patients may refuse available genetic testing, thereby sacrificing improvements in their therapy. The message that must be sent to these patients is that genetic testing for enhancement in drug therapy involves the testing of only certain enzymes or other proteins that are related to a specific therapy, and the results are part of private medical records. A person's genetic information is protected through the Health Insurance Portability and Accountability Act (HIPAA), which was passed by Congress in 1996. Many states also have laws in place that protect the privacy of health information, including genetic data.

Another ethical question involves the allocation of human resources. Some suggest that rather than focus on how genes indicate a predisposition to disease or experiment with ways to change the human germ cell, efforts should be put forth to solve more urgent problems such as worldwide famine or water access. On the other side of the argument are those that speak for the 100,000 hospitalized patients that die annually due to adverse drug reactions and the additional 2.2 million patients that endure non-fatal but serious reactions. Can the obligation of a physician put forth by the Hippocratic Oath be upheld when the information currently available about how drugs will affect specific patients is currently inadequate? Another ethical concern relates to the distribution of burdens and benefits involved in the development of the field. The cost of gene-guided therapy will determine who will have access, and a desire for financial gain among researchers could overpower an interest in either achieving valid data or protecting the well-being of subjects. Also, gaining genetic information for the benefit of a patient may sometimes require access to family health information. If family members refuse to release such information, difficulties in patient treatment may be encountered. 

The pharmacist's role in pharmacogenomics

Given the collection of obstacles discussed, additional work must be accomplished before pharmacogenomic discoveries will find extensive clinical application. First is the need for additional research. Randomized clinical trials must be performed to evaluate the efficacy in improvement of clinical outcomes. Although testing may help inform clinical decisions, overall patient benefit and cost effectiveness have yet to be fully determined. Additionally few guidelines exist addressing the use of particular pharmacogenetic tests, and providers must be educated about pharmacogenomics before we can see its full potential impact to treatment. The rapid changes in this field may result in a provider population that may not feel confident interpreting genetic tests and counseling patients on results. At this time, many researchers in the scientific community are looking to pharmacists as the leaders for the emergence of this new field into clinical practice. With their vast knowledge and understanding of pharmacokinetics and pharmacodynamics, pharmacists are expected to play a key role in applying pharmacogenomic discoveries to patient care. 

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