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Pharmacogenetics: Where Are We Now?

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By utilizing pharmacogenetics to analyze a patient's genetic information, it is possible to predict how well a patient will respond to a given medication, as well as how to optimize the dose and frequency of the medication. It may also be possible to decrease adverse drug events, and thereby personalize and enhance therapy.

Pharmacogenetics: Where Are We Now?
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Introduction
Pharmacogenetics is a rapidly developing field that may lead to increased therapy benefits in patients. Although many may argue that pharmacogenetics will enhance overall patient outcomes for multiple disease states, there are currently many logistical and ethical barriers to its clinical application. Technology, economic factors, education of patients and prescribers and ethical questions are all issues which must be addressed before the use of pharmacogenetics is seen as more mainstream within the health care process. However, there are many benefits to pharmacogenetics, which will likely spur the development of solutions to these issues.

Background
Medication response rates for the treatment of many chronic diseases, such as diabetes and hypertension, range from 30 to 60 percent. These numbers are far from ideal and personalized medicine is seen as a way to optimize a patient’s response rate. The goal of personalized medicine is to look at the patient as an individual and attempt to optimize their drug therapy. A cornerstone of this field is pharmacogenetics, which is defined by the American Association of Pharmaceutical Scientists as “the study of genetic causes of individual variations in drug response.”

Pharmacogenetics is the utilization of a patient’s genetic information to determine how the variations in their DNA lead to changes in their response, metabolism and ideal dosage of various medications and compounds.

In order to understand pharmacogenetics as a whole, it is essential to briefly review genetics. A chromosome is the structural component of DNA, each containing a single DNA molecule. Segments of the DNA molecule are known as genes, and each gene is comprised of nucleotide sequences that are required for transcribing that DNA. These sequences are comprised of four different nucleotides: Adenine (A), Guanine (G), Thymine (T) and Cytosine (C). A series of three nucleotides makes a codon, which codes for an amino acid. When a series of codons is strung together, the amino acid sequence will yield a particular protein.

It has been discovered that over 99 percent of the genetic sequences are identical between individuals, meaning that the genetic variations between us are actually quite small, relative to the entirety of the genome. Variations exist due to polymorphisms, or changes in the sequence of nucleotides. If the variation occurs in a single nucleotide base, it is known as a single nucleotide polymorphism, or SNP (pronounced “snip”). Numeric and alphabetical nomenclature exists to define SNPs. This allows identification of the affected gene in question, as well as the location within that gene in which the SNP occurs. A SNP can also be described as an allele. An allele is the form of a gene which the person possesses. Different allelic subtypes exist for a protein, and possessing different alleles leads to differences in protein expression. Furthermore, each individual inherits two alleles. A patient may be homozygous for an allele, meaning that they have inherited two identical alleles, or heterozygous, meaning that they have inherited two different alleles. These situations may each lead to altered activity of the gene affected by the SNP.

There are several different types of SNPs. A synonymous (or silent) SNP occurs when the change in the nucleotide sequence yields the same amino acid. A nonsynonymous SNP occurs when the change in nucleotide yields a different amino acid. This may or may not impact the protein in question, depending on what amino acid replaces the intended one. Some amino acids will function similarly to the one that was supposed to be present due to chemical properties that determine how it folds and interacts; this leads to minimal change in the function of the protein. Yet another type of SNP is the premature stop codon SNP. In this case, the amino acid sequence that is coded for by the variation in nucleotide sequence codes for a stop, and therefore terminates the protein sequence prematurely. This may or may not impact the function of the protein, depending on where it stops.

The differences in genetic information lead to unique inter-individual characteristics. These differences include hair color, height, disease predisposition and, more importantly for the purposes of this discussion, medication response information. A SNP in a cytochrome P450 (CYP) enzyme may potentially change how drugs are metabolized, changing the pharmacokinetic profile of medications. Also, a SNP in a receptor or target for a medication may change a medication’s pharmacodynamics, thereby changing how that drug interacts with the body. By utilizing pharmacogenetics to analyze a patient’s genetic information, it is possible to predict how well a patient will respond to a given medication, as well as how to optimize the dose and frequency of the medication. It may also be possible to decrease adverse drug events, and thereby personalize and enhance therapy.
The Language of Genetics

<table>
<thead>
<tr>
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<td>Segments of DNA comprised of nucleotide sequences that are required for transcribing that DNA</td>
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Therapeutic Examples

The usefulness of pharmacogenomic (the general study of all of the many different genes that determine drug behavior) testing as applied to medication choice and dosing can be seen in a variety of therapies. Two of the most well-researched of these medication therapies are warfarin and clopidogrel.

Warfarin, a commonly used oral anticoagulant, has attained significant attention due to its narrow therapeutic index and the severe consequences of being outside of the range. The dosing of warfarin is influenced significantly by SNPs in at least two genes, *CYP2C9* and *VKORC1*. Variants to *CYP2C9* that cause decreased metabolism of warfarin are *CYP2C9*2 and *CYP2C9*3 (compared to the wild-type *CYP2C9*1). A study done by Guruprasad, et al., showed that patients receiving low warfarin doses are six times more likely to have *CYP2C9*2 or *CYP2C9*3 variants than patients receiving high warfarin doses. SNPs in *VKORC1* affect the enzyme inhibited by warfarin leading to the drug's anticoagulation properties.

The following table is included in the warfarin insert to guide warfarin dosing based upon presence or absence of the mutant *CYP2C9* and *VKORC1* alleles. *G* refers to the wild type or “normal” form of this enzyme, while *A* refers to the gene with the abnormal SNP.

<table>
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<tr>
<th>Table 1: Three Ranges of Expected Maintenance COUMADIN® Daily Doses Based on CYP2C9 and VKORC1 Genotypes†‡</th>
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<tbody>
<tr>
<td>VKORC1</td>
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<td>--------</td>
</tr>
<tr>
<td>GG</td>
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<tr>
<td>AG</td>
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<tr>
<td>AA</td>
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</table>

† Ranges are derived from multiple published clinical studies. VKORC1-1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

The importance of reaching the target therapeutic INR (international normalized ratio) while on warfarin therapy can be easily rationalized considering the consequences of being either above or below this target. A patient who is below the range may receive subtherapeutic anticoagulation effects, thus failing to reduce the risk of thrombus formation. Conversely, patients who are above the range may be at increased risk of severe bleeding incidents. Schwarz et al. showed that the time to target INR and the time to above range INR were specifically influenced by *CYP2C9* and *VKORC1*.
Clopidogrel is an antiplatelet prodrug that requires activation by CYP2C19 and other CYP enzymes. This CYP gene can have multiple SNPs; CYP2C19*17 is associated with increased function of the enzyme, while CYP2C19*2 is associated with decreased functioning of the enzyme. This means that, theoretically, patients with the CYP2C19*2 allele will not convert enough of the prodrug into the active metabolite, meaning that the clopidogrel would not be producing the optimal antiplatelet function intended. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) trial showed that patients with a reduced function CYP2C19 gene had plasma exposure to the active metabolite relatively reduced by 34.2 percent compared to patients without the reduced function gene. This study also showed that patients with a reduced function CYP2C19 gene were at higher risk for death from cardiovascular diseases than those without the reduced function allele.

**Technology**

The technology surrounding pharmacogenomics is rapidly advancing by the day. One of the most promising technological advances is IBM’s DNA Transistor. IBM is seeking to reduce the cost of gene sequencing from a thousand dollars to a hundred dollars per test by utilizing an approach that consists of threading a DNA molecule through a pore with a diameter of a few nanometers in order to sequence the molecule. While this is occurring, the machine is also translocating the DNA to a privileged area. This model is advantageous in that it is a real time single molecule DNA sequencing method, which requires little sample preparation and low cost. However, there are two obstacles to implementing this new technology – there is no reliable technology to control the translocation of DNA through the nanopore and there are technical difficulties in making small enough sensors. The current solution under development is called a DNA Transistor, a metal/dielectric/metal/dielectric/metal multilayer nano-structure which uses the interaction of discrete charges along the backbone of a DNA molecule while in a modulated electric field to entrap the DNA in the nanopore with single-base resolution. Hopefully in the future, DNA sequencing will become a more affordable health care tool due to continual innovative advances.

**Economics**

One hindrance to the clinical application of pharmacogenomics is the cost. In order to justify requiring patients to undergo testing, one must compare the cost of testing to the cost saved overall, as well as the benefit to the patient’s quality of life. Quality of life is measured as a quality-adjusted life-year (QALY). The extreme limits of QALY are 0 for death and 1.0 for an individual who is in perfect health. Individuals between those limits would be expressed fractionally. A calculation of the cost-benefit itself is seen in the calculation for incremental cost-effectiveness ratio (ICER). ICER is the dollar amount necessary to achieve complete health benefit for a particular intervention. Typically, an intervention is considered cost-effective if it has an ICER of less than or equal to $50,000/QALY.

Warfarin is a great example of a medication that may benefit from pharmacogenetic testing. The Brookings Joint Center for Regulatory Studies conducted an analysis based on a genotype cost of $350 and a 15 percent and 50 percent reduction in bleeding events and stroke, respectively. According to their findings, it was estimated that "formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be $1.1 billion annually, with a range of about $100 million to $2 billion. The researchers came to their conclusion by analyzing the current cost for genetic testing and estimating the costs of various medical events based on existing data. The analysis was based on $250 per test, and approximately $100 per test for labor costs at the facility conducting the test. The article then continues to state their estimation for total net savings, both institutionally and to the individual:

"With full costs of genetic testing of about $350 per test, annual testing costs equal $700 million (2 million tests x $350 per test). We estimate the net health care savings of integrating genetic testing into warfarin therapy to be about $1.1 billion ($1.15 billion in reduced bleeding costs + $675 million in reduced stroke costs - $700 million testing costs). From the standpoint of an individual patient or payer for that patient, the use of genetic tests reduced expected health care by about $900, at a cost of about $350 for an expected net saving of $550. These direct monetary savings substantially understate full social benefits because they do not include the value of the health improvements among warfarin users."

These results seem very optimistic about the benefit of genetic testing for warfarin dosing. However, another analysis based on
three existing studies, done in 2009 by Eckman et al., was far less optimistic. It stated that on the basis of current data and cost of testing (about $400), there is only a 10 percent chance that genotype-guided dosing is likely to be cost-effective (that is, <$50 000 per QALY). It was determined that there was an overall ICER of $170,000/QALY. Upon sensitivity analyses, the study showed that for genetic testing to be cost effective, it would have to be restricted to “patients at high risk for hemorrhage or meet the following optimistic criteria: prevent greater than 32 percent of major bleeding events, be available within 24 hours, and cost less than $200.” This indicates that until the cost of testing decreased, pharmacogenomics testing for most patients would not be cost effective. Reducing the turnaround time from three days to 24 hours is anticipated to reduce the chance (and therefore the cost) of intermittent bleeding prior to receiving test results. Another study by You et al. based cost analysis on a single study, and arrived at an ICER of $357,000/QALY. The analysis concluded that the tests must be below $50 in order to be cost-effective. 

As pharmacogenomics grows, so will the accuracy and validity of testing allowing for an unmistakable benefit of the overall impact of pharmacogenomics on patient care.

Clopidogrel (Plavix®) is another medication that is often discussed in regard to pharmacogenomics. Although few definitive studies have been conducted, very recently Reese et al. created a decision model based on cardiovascular event occurrence in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI). The study utilized a simulated cohort of patients, and analyzed the likelihood of each group experiencing cardiovascular events, bleeding events or no events at all for the 15 months following a PCI. The study found that genotype-guided antiplatelet therapy was dominant, or more effective and less costly, when compared with the selection of clopidogrel [ICER $6,760; 95 percent confidence interval (CI) $6,720 to $6,790] or prasugrel (ICER $11,710; 95 percent CI $11,480 to $11,950) for all patients without regard to genotype.” This indicates that it would be more cost effective to dose all patients based on genetics. However, the study did account for the fact that clopidogrel will be going generic soon, and “cost savings were not evident when genotype-guided therapy that included generic clopidogrel was compared with generic clopidogrel for all patients (ICER $2,300 [95 percent CI $2,290 to $2,320]). Further analyses will be necessary to determine the effect that this plays on the necessity for genetic testing. It should also be noted that it is possible that the sub-study analyses of genotype and the fact that not all study participants used in the analysis had genetic data, may have introduced error into this study. Further studies to determine its validity will be needed.

Education

Education of health care providers about pharmacogenomics poses an obstacle to the advancement of genetics in the medical field. Many doctors and pharmacists graduated from professional programs before the Human Genome project was completed, and many have since graduated without extensive education concerning pharmacogenomics. There are various opportunities, including ACPE (Accreditation Council on Pharmacy Education) accredited continuing education programs, available for pharmacists that wish to receive further training within this growing field.

Ethics

Ethically speaking, pharmacogenomics falls in a gray region. The information that is gathered is of a very sensitive nature, and the donor of the genetic material puts much at risk by giving up their DNA. However, there are a few safeguards in place. Due to The Genetic Information Nondiscrimination Act (GINA), insurers in the group and individual health insurance market cannot use genetic information to increase premiums, deny enrollment, or impose exclusions for preexisting conditions. Insurers cannot request, require or buy genetic information for underwriting purposes and are generally prohibited from asking individuals or family members to undergo a genetic test. However, GINA does not protect against the release of information that pertains to the manifestation of a genetic disease or component. An example would be a dominant gene mutation coding for renal cysts would be protected, while the medical imaging used to find the cysts would not. GINA does not apply to life insurance, disability insurance, long-term care insurance or military health care. Another safeguard in place for patients would be certificates of confidentiality, which allow researchers to resist giving out individual genetic information even under subpoena. This confers perpetual protection even post mortem. Unfortunately, they only apply to data collected while the certificate was active, and ultimately the choice rests with the researcher to disclose or withhold information in the face of a subpoena. This certificate has been tested twice in court, People v. Newman in 1973 and State of North Carolina v. John Trosper Bradley in 2005. The certificate was upheld in both cases.
In the end, even with the protections our government provides, there are flaws in the system. The information here can be sold or exploited to a serious degree; with the burden of privacy falling heavily on the researcher or health care professionals’ sphere of influence. So long as these professionals maintain their integrity, the law should keep personal genetic information as private information.

Conclusion

In spite of the many barriers to clinical application, pharmacogenetic testing may be a valuable asset in determining the proper dose of certain medications, such as clopidogrel and warfarin. By utilizing testing in specifically recommended sub-populations, pharmacogenetics’ necessity may increase, thus warranting further evaluation. As further studies are completed, technological advances continue and more concrete analyses are conducted pharmacogenetics will likely become a more prominent tool in patient care.

References