EXECUTIVE SUMMARY

Millions of people take a variety of drugs every day—but not everyone benefits. Up to 75% of patients may be deemed non-responders to therapy, depending on the disease being treated. In addition, hundreds of thousands of hospitalizations and emergency room visits occur in the elderly population as a result of adverse drug events—a large percentage of which could potentially be avoided. Pharmacogenomics aims to individualize therapy by determining a patient’s genetic make-up and predicting drug response, thus reducing the risk of a potential adverse drug reaction or therapeutic failure.

Pharmacogenomics is the study of how individual genetic differences affect drug response. There is a high level of interindividual difference among the drug-metabolizing cytochrome p450 family. Pharmacogenomic testing can identify which patients may metabolize faster or slower than expected and tailor therapy accordingly. Over 150 FDA-approved drugs across multiple therapeutic areas (e.g., cardiology, psychiatry, oncology) currently have biomarker information in their labeling, allowing for actionable prescribing away from the “one dose fits all” approach.
I. INTRODUCTION

Pharmacogenomics has been defined as the “genome-wide analysis of genetic determinants of drug efficacy and toxicity.” While it may seem so, pharmacogenomics is not a new concept. Its origins can be traced back to the time of Pythagoras (510 B.C.) and his observation that fava beans produced a potentially fatal reaction in some individuals, but not others.

Millions of people take a variety of drugs every day, but not everyone benefits. Up to 75% of patients may be deemed non-responders to therapy, depending on the disease being treated. It is now evident that the “one dose fits all approach” is not working. The term “pharmacogenetics” was coined by Vogel in 1957 and, since then, this rapidly developing field has demonstrated expanded clinical utility in individualizing therapy through maximization of efficacy and minimization of toxicity.

II. SCIENCE

Background

Every human cell (except the gametes) contains 23 pairs of chromosomes that contain all of our genetic information (DNA)—half inherited maternally and half paternally. DNA is composed of nucleotide bases: adenine (A), guanine (G), cytosine (C), and thymine (T). These bases attach in pairs (A with T and G with C) to form the double-stranded helix of DNA. Specific stretches of DNA (small sections of a chromosome), referred to as genes, are responsible for the code of a particular protein. The bases in each gene determine the order in which amino acids will be connected together to form a functioning protein. Occasionally, a variation (mutation) will occur in the order of base pairs and may result in a non-functional protein.

Each chromosome in a pair carries the same genes at the same position. While both versions may code for the same characteristic (ex: eye color), there may be alternative versions of one gene called alleles. Alleles may be the same (homozygous) or they may be different (heterozygous).

The researchers involved in the Human Genome Project sought to analyze the specific sequence of the nucleotides that make up human DNA. With the initial steps completed, it became easier to search for variations in the DNA due to substitution of a base - single nucleotide polymorphisms (SNPs). During the initial sequencing of the human genome, more than 1.4 million SNPs had been identified. Of these, 60,000 occur in the coding region of a gene, potentially translating to a non-functional enzyme that metabolizes a drug or receptor to which a drug binds in order to elicit a pharmacological response. To date, some of these SNPs have been directly tied to various changes in the effects of medications and may even be used to predict clinical response.

Drug Metabolism

Although it has since expanded, the field of pharmacogenomics began with a focus on drug metabolism, which is responsible for converting a drug to metabolites that are more water soluble and therefore more easily excreted. Metabolism may also be utilized to activate prodrugs or may inadvertently create toxic metabolites.

Drug metabolism is carried out by one or more reactions, categorized as phase I (oxidation, reduction, and hydrolysis) or phase II (acetylation, glucuronidation, sulfation, and methylation). While there are over 30 families of drug-metabolizing enzymes, the cytochrome p450 (CYP) family is one that has been well studied.
The Cytochrome P450 Enzymes

The human genome includes 57 CYP genes, classified into 18 families and 44 subfamilies. Although seemingly extensive, only the CYP 1 to 3 families are involved in phase I drug metabolism. This relatively small group is responsible for the observed metabolism of over 90% of all marketed drugs, with CYP3A4/5, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 performing most of the reactions. In fact, CYP3A4 and CYP3A5 metabolize 50% of commonly prescribed medications, while CYP2D6 alone is responsible for the metabolism of up to 25% of medications. To illustrate its complexity, CYP2D6 is encoded by a highly polymorphic gene that has over 70 alleles and 130 genetic variations. The variations in these enzymes can increase or decrease an individual’s ability to metabolize certain drugs, directly affecting the levels of drug found in the body.

Phenotypes

Depending on the types of alleles inherited, an individual can be classified into one of four general and widely recognized phenotypes. Those who are homozygous normal, typically the majority of the population, inherit two normally functioning alleles and are considered extensive metabolizers for that specific enzyme. Intermediate metabolizers (IM) inherit a heterozygous genotype—one functional and one deficient allele—or two partially deficient alleles that result in reduced metabolism. Individuals who lack a functional enzyme and inherit two non-functional alleles are considered poor metabolizers (PM). Alternatively, those who have two or more alleles with extremely high metabolic capacity are categorized as ultra-rapid metabolizers (UM).

III. Statistics / Public Health

Drug response variability in particular is a major clinical problem. In fact, approximately 60-80% of commercially available medications are metabolized by enzymes that are highly polymorphic. As a result, there is a high likelihood that adverse drug reactions and therapeutic failures may be attributed to variations within drug-metabolizing enzymes.

The Centers for Disease Control and Prevention Medication Safety Program estimates that 82% of American adults take at least one medication, with 29% taking five or more; this latter figure increases to 36% for those 75 to 85 years of age. Within long-term care facilities, residents typically average seven to eight different medications per month, with approximately 1/3 of the population taking nine or more. Polypharmacy, typically defined as taking a high number of prescription medications, is associated with issues such as adverse drug reactions, poor adherence, and drug-drug interactions.

Overall, adverse drug events (ADEs) are a serious public health matter. Each year, it’s estimated that ADEs result in 700,000 emergency department visits and 120,000 hospitalizations, attributing to $3.5 billion in extra medical costs. Between 2007 and 2009, there were nearly 100,000 emergency hospitalizations per year in individuals 65 years of age or older that could be attributed to adverse drug events. Two-thirds of these were a result of an unintentional overdose. Alternatively, poor adherence it not without its own set of problems; it has been shown to account for anywhere between 33% and 69% of medication-related hospital admissions in the U.S.

IV. Drug-Drug Interactions

Drug-drug interactions (DDIs) occur between two or more drugs and can alter the way one or both drugs act in the body. These can be pharmacodynamic or pharmacokinetic in nature.

Pharmacodynamic interactions occur when drugs act on the same or interrelated receptor sites. These can result in additive (synergistic, 1+1=3) or antagonistic effects. For example, overstimulation of the 5-HT2A receptor may result in serotonin syndrome and can be due to a combination of an opioid and an antidepressant.
Alternatively, pharmacokinetic interactions tend to be more complex, and involve one drug interfering with the absorption, distribution, metabolism or excretion of another. The cytochrome p450 (CYP) enzyme family is responsible for the hepatic metabolism of drugs and as a result is a major cause of pharmacokinetic drug-drug interactions. Many drugs may act as inducers or inhibitors of the enzymes and effectively change how the enzymes metabolize their substrates. In fact, inhibition may be so strong that a person genotyped as an intermediate metabolizer may react to a drug as a poor metabolizer normally would; the opposite holds true for inducers of the enzymes.

V: Epidemiology

A significant level of interracial variation in the frequency of various alleles has been reported throughout numerous studies and databases. Below is the epidemiologic information surrounding selected cytochrome p450 enzymes:

2D6
PMs represent 5-10% of the Caucasian population; however it is much rarer in Asians and highly variable in Blacks. This phenotype is commonly detected by screening for the *3, *4, *5, and *6 alleles. More specifically, the splice defect resulting in the CYP2D6*4 allele is prevalent in 12-21% of Caucasians but only in 1-2% of Blacks and Asians. IMs, detected by the *9, *10, and *17 alleles, represent a higher percentage than PMs: 10-15% of Caucasians, up to 50% of Asians (typically due to *10), and up to 30% in Blacks (*17 most frequent). The UM phenotype is observed in 1-10% of Caucasians, with gene duplications seen in up to 20% of Saudi Arabians and 29% of Ethiopians.

Drugs commonly metabolized by CYP2D6 include opioids, antidepressants, antipsychotics, and antiarrhythmics. Many of these medications may also have a narrow therapeutic window.

2C19
Although the number of variations identified in CYP2C19 are not as extensive as for CYP2D6, at least 35 variants and a number of sub-variants have been identified. For CYP2C19, the loss-of-function alleles are CYP2C19*2 and CYP2C19*3 while gain-of-function has been associated with *17. CYP2C19*2 has been found in approximately 12-15% of Caucasians, 15% of Blacks, and 29-35% of Asians. The Asian population is also the most likely to exhibit the CYP2C9*3 allele (5-9%), which is present in less than 0.5% of Caucasians. Alternatively, CYP2C19*17 may be present in 16-21% of Caucasians, 3-6% of Asians, and 16% of Blacks.

These polymorphisms may affect drugs such as clopidogrel, proton pump inhibitors, and select antidepressants. Polymorphisms can be associated with a high level of risk when linked to therapeutic failure. Due to the high variation that has been observed with clopidogrel, the FDA added a boxed warning to the approved labeling to emphasize the risks of myocardial infarction and thrombosis associated with the PM genotype.

2C9
To date, over 35 allelic variants have been described for CYP2C9, along with numerous sub-variants. The most common variants, CYP2C9*2 and CYP2C9*3, result in reduced activity for the enzyme and are present in approximately 35% of Caucasians and are relatively rare otherwise. CYP2C9 is responsible for metabolizing drugs which include NSAIDs, sulfonylureas, and phenytoin and therefore has been implicated in bleeding episodes, hypoglycemic episodes, and other therapeutic failures or inefficiencies.
VI. Pharmacoeconomics

In 2001, the U.S. healthcare expenditure was $1.4 trillion and continues to grow at an alarming rate. This figure is projected to be over $4 trillion for 2015. In analyzing what may contribute to such a high number, approximately two million non-fatal adverse drug events cost managed care organizations $5 billion each year.

There have been numerous studies conducted to analyze the potential cost savings that can be seen with the utilization of pharmacogenomic testing. One specific study set out to determine whether patient and clinician access to genetic information during psychiatric treatment selection would influence medication adherence and healthcare costs. The authors found that cases who received genetic testing saw relative cost savings of 9.5% (approximately $562/patient) when compared to the control group. These figures were based on increased medication adherence and a resulting fewer hospital visits.

In another study, Medco patients (n= 3,584, average age of 65) initiated on warfarin were genotyped and compared to a matched historic group. During the six-month follow-up period, the genotyped cohort had 28% fewer hospitalizations due to bleeding or thromboembolism and 31% fewer hospitalizations overall. To put things into perspective, the average hospital stay has been shown to cost $10,000 per day. It is evident that cost savings as a result of increased medication adherence, fewer adverse drug reactions, and fewer hospitalizations can be seen when therapy is individualized to specific genetic results.

VI. CPIC and DPWG

**CPIC**

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in 2009 in order to address the need for specific guidance (for clinicians and laboratories) surrounding the appropriate use of pharmacogenomic testing in the clinic. In order to achieve this, the group—which consists of Pharmacogenomics Research Network members, PharmGKB staff, and experts in pharmacogenomics, pharmacogenetics, and laboratory medicine—has established a framework for understanding the level of evidence needed to justify test incorporation.

The CPIC currently provides in-depth recommendations for 28 FDA-approved medications (although over 150 have biomarker information in their labeling). For instance, the language for amitriptyline, a tricyclic antidepressant, includes the following:

“There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.”

Additional guidelines can be found on PharmGKB.com.

**DPWG**

The Dutch Pharmacogenetics Working Group was established in 2005 in order to develop pharmacogenetics-based dose recommendations and to assist prescribers and pharmacists by integrating those recommendations into systems used for prescribing and medication surveillance. The group consists of clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists, and toxicologists. PharmGKB.com can be utilized to review DPWG recommendations by drug and enzyme groupings.
CONCLUSION

Pharmacogenomics is not a novel concept; over 150 FDA-approved drugs currently have biomarker information in their labeling. As the utilization of pharmacogenomic testing increases, the potential to reduce adverse drug reactions, trial-and-error prescribing, non-compliance, and resulting overall healthcare costs will likely follow suit.

APPENDIX

References


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RADAR-PGx Registry, is working with mutable advanced specialty diagnostic companies, is committed to providing accurate, timely and practical information to physicians through DNA testing in its CAPP / CLIA-certified labs and intuitive, actionable reports. The staff of clinicians assesses the test results and offers treatment recommendations which help physicians make more informed decisions and provide significant value to patients by improving outcomes, reducing severe adverse drug reactions and reducing costs associated with ineffective therapy. For information contact us at RadarPGxStudy@Radar-PGxStudy.com