Personalized Medicine through Pharmacogenetics

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'Personalized Medicine is a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention'

-World Health Organization (WHO), 2013

Introduction

Physicians have long been aware of the subtle differences between patients in their responses to medications. The recognition that a part of this variation is inherited, and therefore predictable, created the field of pharmacogenetics several years ago.

Pharmacogenetics studies the influence of genetic variation on drug response. Knowledge of gene variants causing differences in drug response among patients has the potential to allow 'personalized' drug therapy.

A patient's response to a drug is often linked to common genetic variations present in their genes. One type of genetic variation is the single nucleotide polymorphisms (SNPs). Knowing the types of SNPs/genetic variations present in a patient can help predict the associated drug response. This can not only help physicians individualize drug therapy, it will also help improve effectiveness of the drug, decrease the chance of negative side effects and save healthcare costs.[1]

Accurate prediction about drug response is crucial for individualized treatment. This is best made by combining an individual's genetic data with clinical findings and classifying individuals into subpopulations that differ in their response to a specific drug.[2] Using this approach, health care providers may be better equipped to move beyond the "one-size-fits-all" treatment strategy that defined much of patient care in the past, to care that is appropriate for unique patient subgroups.

Figure 1. Patient-centric model of care in personalized medicine
www.cpmc1.coriell.org/personalized-medicine (Coriell Institute)

Pharmacogenetics	Pharmacogenomics
Studying an individual's variations in genes involved in drug metabolism is termed pharmacogenetics.	The term pharmacogenomics, which often is used interchangeably with pharmacogenetics, refers to the application of genomic technologies to the study of pharmacogenetics.

The discovery of genetic factors such as the cytochrome P450 (CYP) drug metabolizing genes and several years of subsequent clinical research have added to our understanding of the clinically relevant genetic variations that may help predict drug response.

Genetic variation, an important determinant of drug response

The type of medication and optimum dose required for effective and safe therapy varies significantly from patient to patient. Factors that cause variation in drug responses are complex involving genetic, environmental and physiological factors (Table 1).[3,4]

Table 1: Factors Causing Variability in Drug Responses

Genetic factors - Mutations in genes for drug-metabolizing enzymes, drug transporters and targets
Environmental factors - Chemicals, co-administered drugs, diet, tobacco smoking & alcohol use
Physiological factors - Age, sex, and disease status

Genetic factors are generally permanent as variations in genes are inherited and stable over the course of lifetime. However, the impact of environmental and physiological factors on drug response is transient in most cases.

Genetic variation is considered an important source of variability in drug response and contributes to 25% - 50% of inappropriate drug responses.[5] It has the potential to negatively impact effectiveness of drug therapy ('drug efficacy') and increases the risk for dangerous side effects, termed adverse drug reactions (ADRs).

Linking the genetic source of variability to drug response is often clinically significant and meaningful.[3, 6]

Genetic Variation and Drug Efficacy

The extent to which patients metabolize drugs have significant impact on the **effectiveness of their pharmacologic therapy**. For example, individuals with genetic variation that results in ultra-high metabolism of drugs can experience therapeutic failure on standard dose of drug, due to rapid clearance of the drug from their system.

Typical drug efficacy rates range from 25% to 80%, with most drugs falling in the range of 50 to 60%.[5] For example, only 50-60% of patients experience improved outcome with drug therapy used for depression, schizophrenia and cardiac arrhythmias (Table 2).[7]

Table 2: Drug Efficacy Rates For Major Drugs in Selected Therapeutic Areas

Therapeutic Area	Efficacy rate (%)
Cardiac arrhythmias	60
Schizophrenia	60
Depression (SSRI)	62
Analgesics (Cox-2)	80

Genetic variation also plays a crucial role in **drug-drug interactions**. Presence of a second drug may induce (enhance) or inhibit the metabolic activity of a certain enzyme responsible for drug metabolism. Such unwanted drug-drug interactions can influence the activity of the CYP enzyme and reduce bioavailability of the primary drug being taken. If this occurs in a patient with low initial level of enzyme activity due to genetic variation, drug-drug interaction can result in poor efficacy and dangerous side-effects.[8]

Identifying genetic variations ('genotyping') in drug-metabolizing enzymes has led to physicians improving the dosing of drugs for conditions as wide-ranging as depression and anxiety, coronary and peripheral artery disease, inflammatory bowel disease and cancer, thereby helping patients avoid ineffective treatment.[2]

Genetic Variation and Adverse Drug Reactions (ADR)

Adverse drug events due to variability in drug responses are often preventable causes of medical injuries[9] and remain an underappreciated clinical issue. The FDA Adverse Events Reporting System (FAERS) estimated 800,000 ADRs in the U.S. and Europe combined for the year 2011.[10] The incidence of serious & fatal ADRs has been rising with the increase in the number of medications prescribed. An estimated $3.5 billion is spent on additional medical cost associated with ADRs annually and at least 40% of this may be preventable.[11]

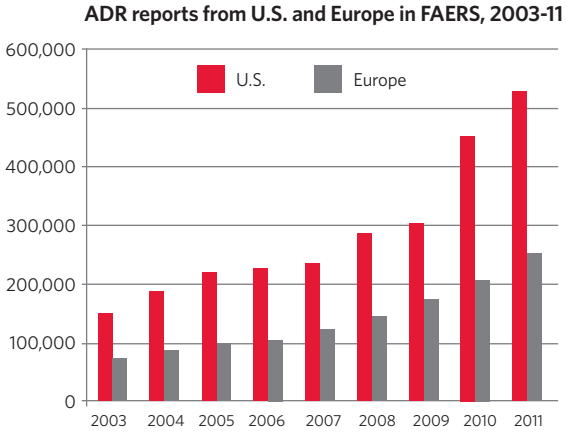

Figure 2. ADR reports from U.S. and Europe in the FDA Adverse Events Reporting System (FAERS), 2003-2011

ADRs are commonly seen in patients with low CYP enzyme activity leading to serious clinical consequences. Pro-drugs that have not been metabolized can lead to high plasma levels of the drug with unpleasant side-effects or life-threatening complications from toxin levels of the drug. A deleterious cascade effect can also result from drug-drug interactions due to simultaneous administration of multiple medications that are metabolized by the CYP enzyme.

Genotyping provides an understanding of the genetic factors that may contribute to variability in drug response and can help maximize the likelihood of efficacious treatment, and minimize ADRs.[5]

Genes Involved in Drug Metabolism

There are several genes responsible for differences in drug metabolism and response. Among the most common are the cytochrome P450 (CYP) genes. They encode the cytochrome P450 class of metabolic enzymes found primarily in the human liver. Many of these enzymes play an instrumental role in the breakdown and clearance of clinically prescribed drugs. Up to 80 percent of prescription drugs are metabolized by the 5 main cytochrome P450 enzymes, CYP2D6, CYP2C19, CYP2C9 and CYP3A4/5.[12]

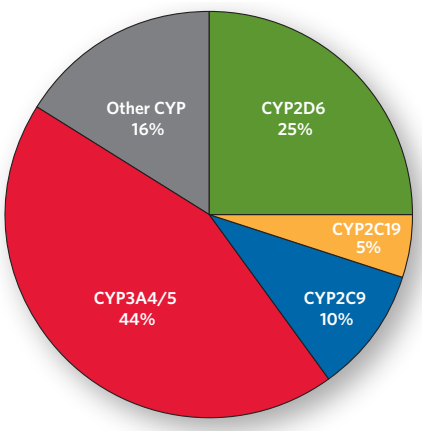

Figure 3: Relative importance of polymorphisms in human cytochrome P450 enzymes involved in drug metabolism

The Food and Drug Administration (FDA) maintains a listing of drugs for which pharmacogenetic biomarker information is included in the drug label. Table 3 is a partial list of those FDA-approved drugs categorized by therapeutic area with the corresponding pharmacogenetic biomarker involved in the metabolism of that drug.

Table 3: Common Drugs Metabolized by CYP2D6, CYP2C19 and CYP2C9

Genetic Marker	Therapeutic Area	Drugs
CYP2D6	Psychiatry	Citalopram, Fluoxetine, Paroxetine, Venlafaxine, (numerous)
	Cardiovascular	Carvedilol, Metoprolol, Propranolol, (others)
	Derm and Dental	Cevimeline
	Analgesics	Codeine
CYP2C19	Musculoskeletal	Carisoprodol
	Psychiatry	Citalopram, Diazepam, Fluvoxamine
	Neurology	Clobazam
	Cardiovascular	Clopidogrel, Prasugrel
	Gastroenterology	Esomeprazole, Omeprazole, Pantoprazole
CYP2C9	Analgesics	Celecoxib
	Psychiatry	Fluvoxamine
	Hematology	Warfarin

The safety and efficacy of these drugs are affected by genetic variations present in these CYP genes. For example, a class of antidepressants called selective serotonin reuptake Inhibitors (SSRIs) are often the first-line choice for depression therapy in the United States. Unfortunately, the benefits of treatment take 2–4 weeks to begin, and only 50 to 60% of patients experience improved outcome. Current use of SSRIs is highly empirical, with clinicians and patients often going through several trials of drug choice and dosing. Cytochrome P450 enzymes CYP2D6 and CYP2C19 are the primary enzymes involved in the metabolism of SSRIs. Using a pharmacogenetic test prior to administering therapy may help determine the most effective SSRI therapy, shorten time to clinical response and improve quality of life.[7]

Conclusion

Laboratory techniques to detect drug response variability exist currently. Phenotyping and /or genotyping are primary methods used. Phenotyping is carried out by measuring enzyme activity directly using a probe drug whose metabolism is known to be solely dependent on the particular CYP enzyme. However, using a probe drug to measure individual phenotypes has limitations. Measuring concentration at various time points requires collecting multiple specimens at fixed times (typically at 8-hours post-administration). The individual is also exposed to possible unfavorable side effect of the probe-drug. Additionally, the metabolism of the probe drug may be affected by interfering drugs, disease status and other environmental factors (such as a patients overall health, weight, age, diet).

The drug-metabolizing phenotype of an individual can also be predicted using assays that determine genotype from a patient sample. Genotyping results are not affected by drugs, diet or environmental factors. Genotyping assays by molecular methods are fast, reliable and accurate. The interpretation of the genotype result to the phenotype is based mainly on literature, and on the physician's judgment.

Identification of patient genotypes for clinically relevant CYP genes can help physicians tailor drug treatment to patients through the selection of appropriate therapies. These measures may improve a physician's ability to impact patient outcome by ensuring maximum drug efficacy with minimal adverse drug reactions.[13]

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