Precision medicine

Pharmacogenomics: What is it, and why is it important?

Keywords
Drug metabolism, pharmacogenomics (PGx) testing, personalized medicine, adverse drug event (ADE)

Introduction

In this white paper, we:

- Define pharmacogenomics
- Describe how genotypes influence drug metabolism
- Provide examples of how genotyping influences drug choices
- Describe how pharmacogenomics may help reduce medical costs

What is pharmacogenomics?

Although modern medical science has developed an extensive pharmacopeia to target a wide variety of pathologies, we know that not everyone will respond the same way to a given drug (Figure 1). Some individuals will experience the desired outcome, some individuals will have a limited response or none at all, and others may suffer adverse drug events (ADEs). ADEs are unintended and harmful side effects that range from relatively mild discomfort (e.g., nausea) to organ damage and other life-threatening outcomes. ADEs can result from an individual's genetic makeup, specifically the genes that encode drug-metabolizing enzymes (DMEs).

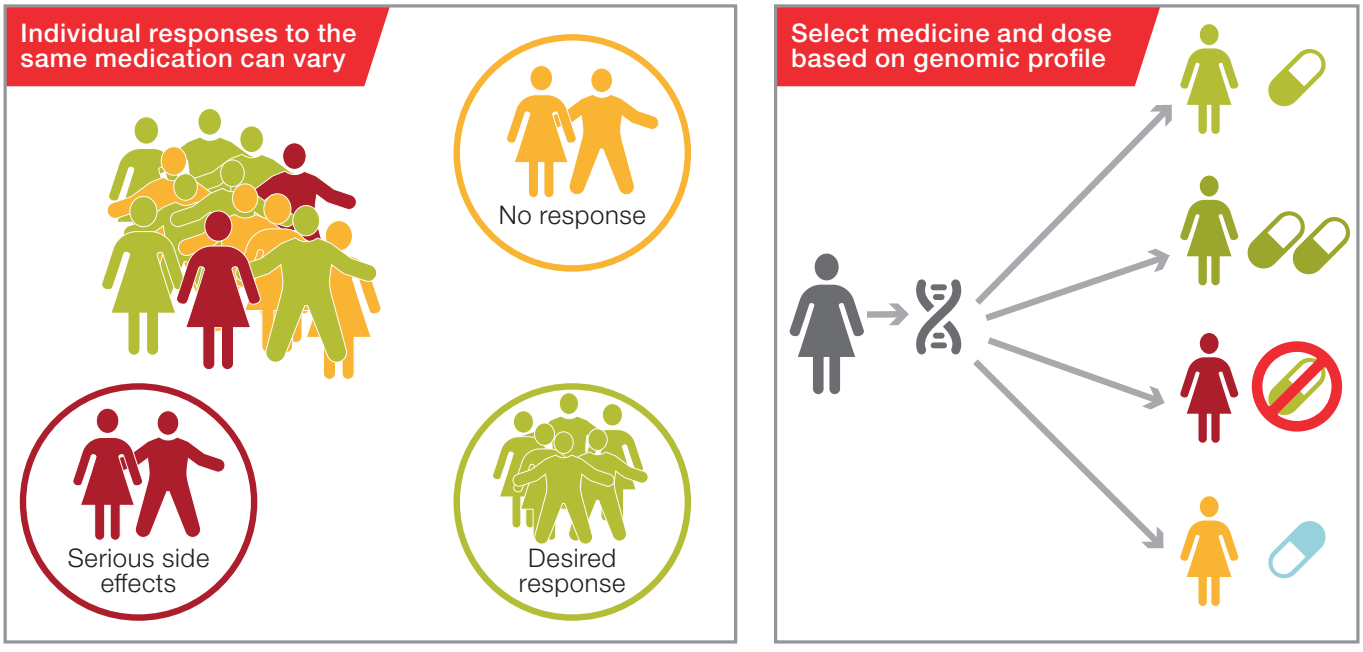

Figure 1. Pharmacogenomics attempts to match the drug-related metabolic genotypes of individuals with appropriate drugs and dosages. **Left:** Some individuals in a population will have the desired response to a drug, but others may not respond to the drug at all or experience serious side effects. **Right:** Some individuals will respond to a drug at the standard dose (light green), while others may require twice as much for the drug to be effective (dark green). Some individuals might have serious reactions and should not take the drug (red), and some individuals may not respond and require a completely different drug (yellow).

Pharmacogenomics (PGx) combines knowledge about drug metabolism pathways and genomics to understand how individual genetic profiles influence responses to medications. The goal of pharmacogenomic analysis is to match a drug to a person's DME-related genetic makeup. Simply stated, PGx holds the promise of ensuring the right drug is administered to the right patient at the right dose. This includes determining whether a drug might be harmful and best avoided or simply ineffective and if a different strategy might be appropriate. PGx also attempts to inform the proposed treatment regimen to mitigate the risk of ADEs and increase the likelihood of seeing the treatment through to completion. This approach has the potential to produce better outcomes for patients, because healthcare providers can administer the most appropriate and effective treatments based on the unique genetic characteristics of their patients.

How are drugs metabolized?

When drugs are administered, they undergo a complex journey through the body that begins with absorption into the bloodstream. Once in circulation, drugs are generally transported to the liver, which is the primary site of drug metabolism. Some enzymes in the liver convert lipophilic drugs into more hydrophilic metabolites, making them easier to excrete. Others convert drug precursors (prodrugs) to active molecules. After drugs are acted on in the liver, the metabolites are transported through general circulation to target organs where they can have their intended effects. Eventually, the kidneys and intestines remove the drug metabolites from general circulation (Figure 2).

The cytochrome P450 (CYP450) family of enzymes comprises extremely important phase I drug metabolizers that are predominantly expressed in the liver [1]. Many of these enzymes are monooxygenases that introduce oxygen atoms, typically resulting in the conversion of lipophilic drugs to more hydrophilic metabolites. Enzymatic conversion can either transform an inactive prodrug to an active drug that can have the desired biochemical effect or inactivate a drug and facilitate its excretion from the body.

In phase II metabolism, enzymes called transferases conjugate small-molecule drugs to polar functional groups. These enzymes include UDP-glucuronosyltransferases (UGTs), sulfotransferases, glutathione-S-transferases (GSTs), and a host of other transferases [2]. Like CYP450 enzymes, phase II transferases help increase the hydrophilicity and availability of drugs but may also produce toxic by-products [3].

Other proteins that are important for drug activity are phase III transporter proteins. The SLC22 family of transporter proteins has a central role in transporting small molecules between tissues and interfacing body fluids [4]. Because these proteins are so important for drug metabolism, the SLC22 family is one of the most studied drug transporter families in pharmacodynamics [5]. P-glycoprotein (P-gp), also known as multidrug resistance protein 1 (MDR1), is another transporter protein. P-gp is an efflux transporter that influences the absorption, distribution, and elimination of toxins and xenobiotics, primarily from blood circulation into brain cells and from the intestinal lumen into epithelial cells [6,7].

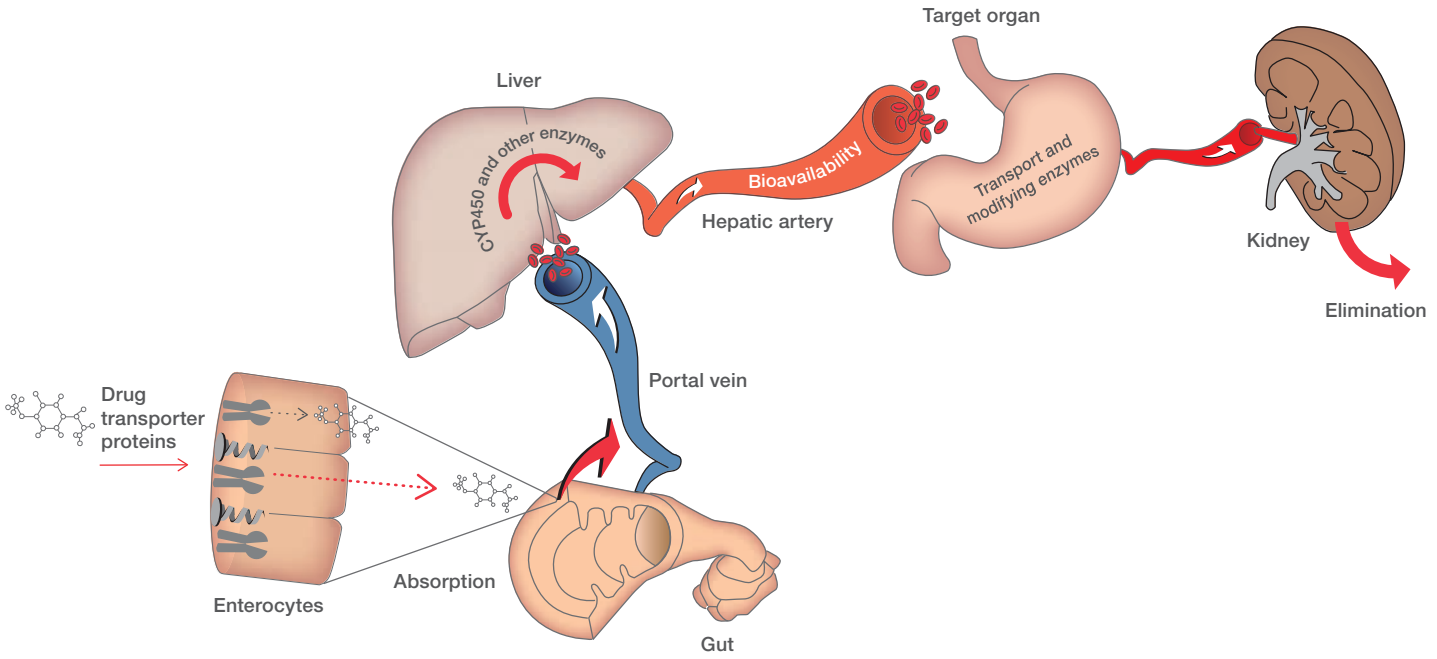

Figure 2. General drug metabolism pathway. A drug that enters through the gut is passed through circulation to the liver. Phase I and phase II enzymes in the liver modify the drug, and the modified drug (metabolite) circulates to the target organ. The metabolite is finally filtered from circulation by the kidneys, after which it can be excreted. Some drugs have different metabolic pathways.

How does genotype influence drug metabolism?

Like all DNA, the genes that encode DMEs and other proteins that interact with drugs are subject to mutations that can affect protein function. Fortunately, these mutations can be detected easily with common genetic analysis techniques, and individuals can be readily genotyped using blood samples or buccal swabs. Mutations in DME genes can be broadly categorized in terms of how they affect the quantity of active enzyme. They can either result in loss of function or gain of function, or be neutral. A loss-of-function mutation can reduce or eliminate enzymatic activity by interfering with the function of an enzyme or expression of the mRNA that encodes it. Conversely, a gain-of-function mutation can increase enzymatic activity by removing inhibitory control over expression of a gene that encodes an enzyme. Although rare, a gain-of-function mutation can also make an enzyme more efficient. Neutral mutations are sequence changes that have no effect on protein function or abundance.

Mutations can also be grouped into the four categories listed in Table 1. Single nucleotide polymorphisms (SNPs), also known as single nucleotide variants (SNVs), are variations at single nucleotides in DNA sequences. A SNP that falls in the coding region of a gene can change the amino acid sequence, and consequently the function, of the protein the gene encodes. If a SNP falls in a promoter or enhancer region, it can alter when, where, and how much protein is synthesized. Insertions and deletions (indels) are mutations involving one or a few nucleotides. Indels have more impact when they occur in coding sequences because they can cause reading frame shifts, which change the amino acid sequences downstream and may introduce premature stop codons. A copy number variant (CNV) is the result of deletion or duplication of an entire gene or region within a gene. These mutations can alter the amount of protein produced by cells and usually occur in the germline, so they are distributed uniformly in all tissues.

The amount of functional enzyme in a cell is also affected by the allelic makeup of the individual. Every cell contains two copies of each gene on autosomal chromosomes, and each copy (allele) can contain any of the sequence variations described in Table 1. If both copies of a DME gene encode a normally functioning enzyme, drug metabolism by that enzyme will be normal. However, if one allele encodes the normally functioning enzyme and the other contains an inactivating mutation, the activity of the enzyme will be lower by half. Conversely, having one normal allele and one allele with a CNV duplication can increase the activity of the enzyme by 50%. There may be no active enzyme at all if both alleles contain inactivating mutations.

Different combinations of alleles can result in a spectrum of enzymatic activity, and it is often convenient to describe individuals based on the amounts of active enzyme they have. For example, particular *CYP2D6* allele combinations can make an individual an ultrarapid metabolizer (UM) with elevated enzymatic activity, an extensive (normal) metabolizer (EM) with average enzymatic activity, an intermediate metabolizer (IM) with low enzymatic activity, or a poor metabolizer (PM) with no enzymatic activity [8]. Such phenotypic characteristics are used to describe a response to a drug, and knowing an individual's metabolizer phenotype is critical to ensuring the right drug is administered at an appropriate dose.

Pharmacogenomics researchers use star allele nomenclature to refer to alleles. In this system, alleles are not identified by the positions of variants in cDNA, genes, or proteins (e.g., g.27289C > A or p.T398N); instead, an allele is denoted by the name of the gene followed by an asterisk and a number. For example, *CYP3A5*2* identifies the g.27289C > A variant in the *CYP3A5* gene, which encodes a CYP enzyme with a T398N mutation. Star allele nomenclature can simplify reference to important alleles and accommodate haplotypes with multiple mutations that are tightly linked. This nomenclature also makes it easy to describe heterozygotes (e.g., *CYP3A5*2/*5*).

Table 1. DNA sequence variants that are commonly found in DME alleles with different activities.
Green text: normal sequence; red text: altered sequence; * indicates a stop codon.

	Definition	Effect	Example
Coding SNP	Replacement of one nucleotide for another in a coding region	Can reduce or eliminate the enzymatic activity of a protein	AACGCT -----> AAGGCT AsnAla -----> LysAla
Promoter or enhancer SNP	Replacement of one nucleotide for another in a promoter or enhancer region	Can change the expression level of a protein	TATAA -----> TAGAA Mutation in TATA box (transcription cannot begin)
Indel	Loss or gain of one or a few nucleotides	Can introduce translation frameshifts, most likely eliminating function	AACGCTTTAG -----> AACG_TTTAG AsnAlaLeu -----> AsnVal*
CNV	Loss or gain of a region containing an entire gene	Can increase or decrease the quantity of a protein	GeneA -----> GeneA–GeneA (1 copy -----> 2 tandem copies)

What are some examples of benefits for patients?

Oncology: tamoxifen

Tamoxifen in breast cancer patients is one of the best examples illustrating how pharmacogenomics can provide drug dosing guidance. Tamoxifen is an estrogen receptor antagonist in breast tissue, and it is commonly used to treat certain types of breast cancer. Tamoxifen is acted on by several DMEs (*CYP2D6*, *CYP3A4*, *CYP3A5*) [9], and some of the metabolites can have 100 times more antiestrogenic activity than tamoxifen itself [10]. Tamoxifen may be less effective for individuals who have DME alleles that make them intermediate or poor metabolizers, because they cannot efficiently convert tamoxifen to these active metabolites (Figure 3) [11]. For this reason, several organizations recommend testing and consideration of alternate treatments for these individuals [12].

Pharmacogenomics can also help patients manage the side effects associated with tamoxifen treatment. Tamoxifen side effects include nausea, anxiety, hot flashes, and pain, so they can cause a patient to seek additional medication and ultimately influence whether the patient stays the course of a tamoxifen treatment regimen. In a study of breast cancer patients in Sweden, He et al. identified a strong correlation between *CYP2D6* metabolizer genotype and the use of symptom-relieving medications by patients receiving tamoxifen [13]. A larger proportion of ultrarapid metabolizers used symptom-relieving drugs, and a significantly larger proportion of ultrarapid metabolizers discontinued tamoxifen treatment (Figure 4). The side effects of tamoxifen can be managed by adjusting the dose to match the patient's *CYP2D6* genotype, which increases the likelihood that the patient will get the full benefits of complete tamoxifen treatment.

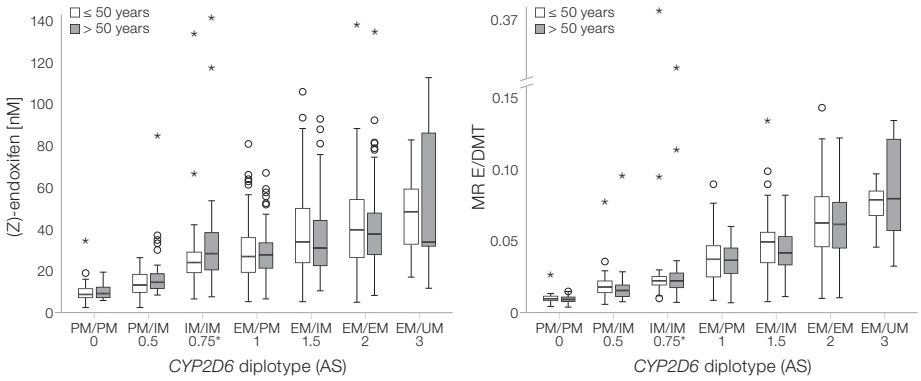

Figure 3. *CYP2D6* genotype affects quantities of active tamoxifen metabolites [11]. Tamoxifen is transformed in the liver to (Z)-endoxifen, which has potent antiestrogen effects. The patient plasma concentration of (Z)-endoxifen (left) and the metabolic ratio of (Z)-endoxifen to desmethyl-TAM (E/DMT, right) depended on *CYP2D6* diplotype and age in 897 patients. PM: poor metabolizer; IM: intermediate metabolizer; EM: extensive (normal) metabolizer; UM: ultrarapid metabolizer. PM and IM patients had lower levels of endoxifen, suggesting higher doses of tamoxifen would be needed to be effective.

From Schroth W et al. (2017) Improved prediction of endoxifen metabolism by *CYP2D6* genotype in breast cancer patients treated with tamoxifen. *Front Pharmacol* 8:582 (**doi:10.3389/fphar.2017.00582**). This article is distributed under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**.

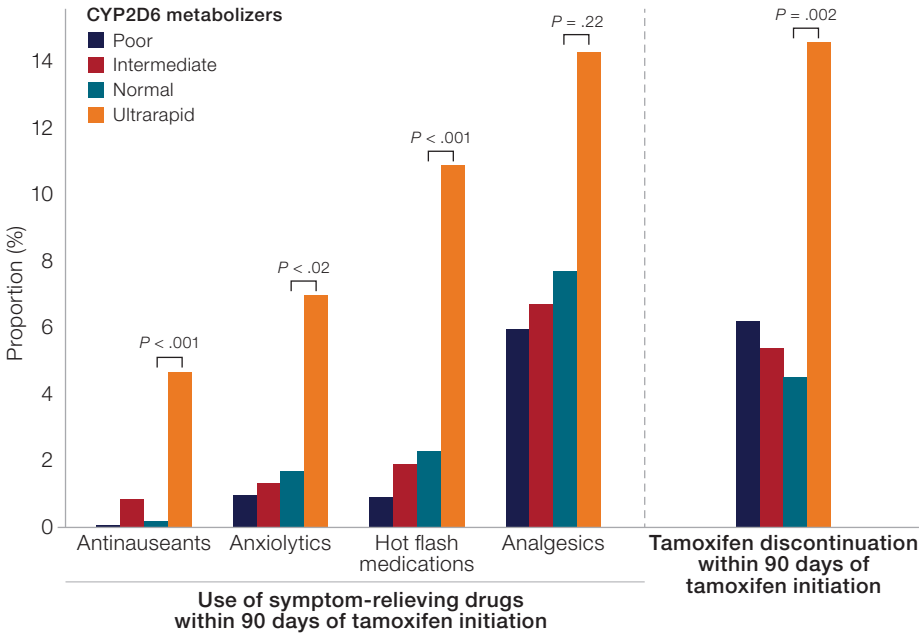

Figure 4. CYP2D6 metabolizer status influences discontinuation of tamoxifen use in breast cancer patients [13]. There was a trend towards increasing use of symptom-relieving drugs coincident with *CYP2D6* haplotype. Use was defined as any prescription of a symptom-relieving drug within 90 days of tamoxifen initiation.

From He W et al. (2020) *CYP2D6* genotype predicts tamoxifen discontinuation and prognosis in patients with breast cancer. *J Clin Oncol* 38(6):548–557 (**doi:10.1200/JCO.19.01535**). This article is distributed under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**.

Psychiatry

Psychiatric disorders encompass a wide variety of abnormal brain functions. Some psychiatric disorders can be treated with certain drugs, but drug efficacy is difficult to predict due to genetic heterogeneity and unrelated adverse events [14]. Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression, anxiety, and other psychiatric conditions. However, only about half of patients respond to SSRI therapy, and several weeks of administration are often required before it can be determined whether treatment is effective [15]. Many studies have identified loci that are implicated in SSRI responsiveness [16]. The results of these studies indicate that knowing which *SLC6A4*, *HTR1A*, *HTR2A*, *BDNF*, and *ABCB1* alleles an individual carries before SSRIs are administered may allow for modulation of the SSRI response and limit adverse events. To facilitate this, machine learning techniques are being coupled with pharmacogenomic analysis to better predict links between genotype, effectiveness, and adverse reactions [17].

Schizophrenia is a debilitating mental illness that can be treated with drugs such as olanzapine, aripiprazole, and risperidone. However, these drugs can induce a variety of adverse drug reactions, including hyperprolactinemia, tremor, akathisia, dystonia, anxiety, and distress [18]. They are metabolized by cytochrome P450 and other enzymes, and the genotypes of the corresponding loci have been found to be important in the response. Soria-Chacartegui et al. suggest that pharmacogenomic analysis could reduce the frequency of adverse reactions and facilitate better outcomes [18].

Pain management

Opioids and cannabinoids are used in palliative care to control pain and other symptoms of harsh treatments and chronic conditions. In many cases involving this type of care, particularly cases that require aggressive intervention, there is little time to spend on traditional trial-and-error approaches to find a drug regimen that provides effective symptom relief. Pharmacogenomics can help providers find the best options for treatment in a more timely manner. For example, codeine is metabolized into active morphine by CYP2D6 [19], which is strongly influenced by the *CYP2D6* allele. Codeine can be expected to have poor analgesic effects in individuals who are poor metabolizers; conversely, ultrarapid metabolizers may experience severe respiratory depression [20,21].

Cardiology

Cardiovascular disease is a major contributor to morbidity around the world. Each year in the United States alone, approximately 690,000 individuals will have an ischemic stroke, and approximately 240,000 more will have a transient ischemic attack [22,23]. Although antiplatelet and anticoagulant therapies can reduce the risk of cardiovascular disease, there is still variation in patient responses to these drugs that must be accounted for when considering dosage options [24].

Clopidogrel is used to treat stroke and other cardiovascular ailments. It is a prodrug that is metabolized, mostly by CYP2C19, to an active drug that inhibits platelet activation. Genetic variation at the *CYP2C19* locus can dictate how effective a clopidogrel dose will be. For example, it takes three times the dose of clopidogrel to achieve the same platelet inhibition in intermediate metabolizers as in normal metabolizers, and even four times the dose is insufficient in poor metabolizers [25]. Conversely, gain-of-function mutations in *CYP2C19* that result in an overactive enzyme can lead to excessive bleeding [26]. Thus, knowing the allelic configuration of *CYP2C19* can guide dosage requirements.

Warfarin is an anticoagulant that works as a vitamin K antagonist. Warfarin metabolism depends on the activity of the *CYP2C9* gene [27], and genetic variants are estimated to account for 30% to 40% of the variability in responses to warfarin treatment [28]. Currently, a best-guess approach is used to determine warfarin dose, and individuals are monitored and dosages adjusted frequently to maximize efficacy and minimize the risk of adverse effects. Efforts are underway in several clinical trials to investigate correlations between genotypes at various loci and optimal warfarin dosages [29,30].

Are there guidelines for implementing pharmacogenetic testing?

Successful implementation of pharmacogenetic testing relies on translating genetic laboratory test results into actionable prescribing decisions for relevant drugs [31]. Several organizations collect pharmacogenomic data, including DME genotypes and information about their influence on small-molecule metabolism. The goal of the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** is to facilitate implementation of pharmacogenetic testing by creating, curating, and publishing freely available, peer-reviewed, evidence-based, updatable, and detailed gene and drug clinical practice guidelines. For example, the CPIC has recently published a guideline in which they describe the effect of genotype on SSRI effectiveness and review testing options [32]. A number of national agencies have taken advantage of the **Pharmacogenomics Knowledgebase (PharmGKB)** to establish organizations based on guidelines for alleles that are common in their populations. These organizations include the **Dutch Pharmacogenetics Working Group (DPWG)**, the **French National Network of Pharmacogenetics (RNPGx)**, and the **Canadian Pharmacogenomics Network for Drug Safety (CPNDS)**. The **Association for Molecular Pathology (AMP)** has issued guidelines for standardization and implementation of pharmacogenetic testing in clinical laboratories to help ensure that tests are accurately validated, interpreted, and reported [33]. Additional information and guidance for implementing pharmacogenetic testing can be found in the literature [34-36].

How can pharmacogenetic testing reduce costs and improve outcomes?

Rising healthcare costs are driving demand for ways to reduce costs and improve outcomes, both of which are important to patients, healthcare providers, payers, healthcare systems, and society. Pharmacogenetic testing and the follow-on matching of drug to genotype can help drive down healthcare costs and improve outcomes [37]. It reduces the need for a trial-and-error approach to drug delivery in which a drug or dose is tried, the effects are evaluated, and adjustments are made. This approach often requires a patient to visit a hospital or clinic multiple times for evaluation and adjustment before the right combination is found. The cost of repeat visits adds up, and being able to identify the right drug and dose at the start can help reduce this cost. A recent study estimated the savings that would be realized by pharmacogenetic testing for depressive disorders and concluded that close to $900 million could be saved over 20 years [38].

Discomfort from an ADE can cause a patient to discontinue treatment before completing it or force the patient to take auxiliary drugs to treat side effects, further driving up costs. In some cases, hospitalization is required to treat ADEs and allow patients to recover. In the worst case, an ADE might result in loss of life. Pharmacogenetic testing may help reduce the frequency of ADEs, their associated costs, and the likelihood of patients discontinuing treatment [39,40].

A large fraction of the price of a drug comes from the clinical trials required to develop the drug, and clinical trials often require large subject cohorts to achieve statistical significance. Pharmacogenetic testing may help clinicians identify patients who are likely to successfully metabolize the drug for the desired effect during development. Preselecting such patients and eliminating those who will not benefit from the drug might reduce the size of the cohort required for testing. This could expedite release of the drug, making it available to those who can benefit most and potentially reducing the cost of the drug.

Conclusion

It is clear that an individual's genomic profile can significantly influence how they metabolize drugs. Pharmacogenetic testing of drug metabolizer and transporter genes can identify a person's allelic makeup and predict their drug metabolizer phenotype. With this information, clinicians may be able to adjust drug choice and dose accordingly. Pharmacogenetic testing thus has the potential to help patients benefit from therapy faster with fewer side effects and ultimately bring down costs, making it an increasingly important aspect of personalized medicine.

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