Pharmacogenomics: What the Doctor Ordered?

by Joel C. Eissenberg, PhD & Rajeev Aurora, PhD

The growing understanding of genes that control metabolism of specific drugs, combined with a comprehensive genotype of each patient, offers "precision medicine" in a very literal sense.

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Abstract

About half a million adverse drug reactions are reported in the US each year that result in disability, hospitalization or death. The efficacy or toxicity of a drug in a patient can be strongly influenced by their genetics as well as environment. Application of genomics to clinical pharmacology, "pharmacogenomics," promises to transform patient care and health resource utilization in the coming decade.

Introduction

Completion of the human reference genome sequence, together with the advent of inexpensive DNA sequencing and ever more powerful computers, have converged to open a new era of precision medicine. Precision medicine is defined as medical care tailored to optimize efficiency or therapeutic benefit for individuals or specific groups of patients. Applications of precision medicine include defining risk for disease (genomics), defining vulnerabilities of specific cancers (oncogenomics) and defining response to drugs (pharmacogenomics).

The observation that people can differ significantly in their response to the same drug or compound is not new. The Greek philosopher Pythagoras noted in 510 BCE that only some people who ate fava beans developed potentially fatal hemolytic anemia.[1] The English physician, Sir Archibald Garrod, was the first to suggest that genetic variation might underlie variability in drug action.[2] By the 1960s, genetic variability in patient responses to several clinically important drugs had been noted, formalizing the field of pharmacogenetics, the study of how a specific drug is affected by alleles of a specific gene.[3] With the arrival of inexpensive genome sequencing, the single-gene associations of pharmacogenetics have been expanded to surveys of entire genomes, hence pharmacogenomics.

Here, we summarize current insights gained from pharmacogenomics and their potential impact on medical practice.

A Brief Introduction to Pharmacology

A drug therapy can produce one of three responses: first, the patient can have the expected normal response resulting in the lowering of pathology and/or symptoms. Second, a patient can be a non-responder where no beneficial effect on the disease or symptoms is observed. Finally, a patient can have an adverse response ranging from developing a mild cough to mortality. A central goal of pharmacogenomics is to reliably predict from the patient's genome which response is expected. Non-response arises because the drug is unable bind to its target. Non-binding may be due to alterations

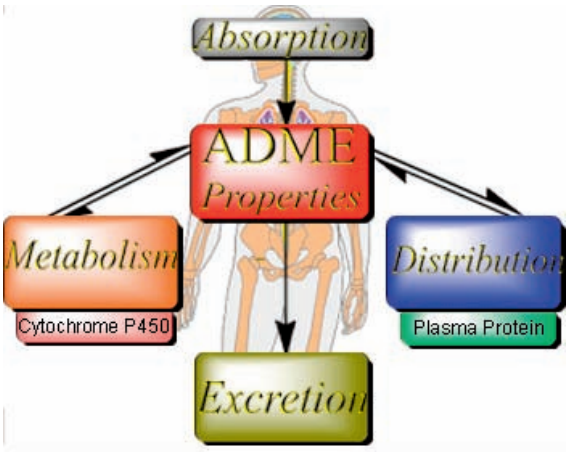

Figure 1

From: https://moulder.temple.edu/research-capabilities/vitro-adme-and-pharmacokinetics

(mutations) of the drug's binding site in the target. Bacteria and especially viruses have high mutation rates to evade seletion pressure of the immune system. Mutations in drug binding sites are more prevalent with antibiotics and antivirals because of the selective pressure of the drug. In addition, these organisms acquire antibiotic resistance genes. Changes in target sequences is also common in antineoplastic drugs because tumors also rapidly accumulate mutations due to genomic instability. Outside these situations, sequence variation in the patient population in the drug target binding site (e.g. in a receptor, kinase, or enzyme) does occur as well that can prevent binding of the drug. A second reason for non-response is that the drug concentration is below the level needed to produce efficacy of inhibition (antagonism) or activation (agonism). In contrast, often (but not always) adverse responses arise because of high concentration, causing off-target effects or directly dysregulating a pathway. The therapeutic concentration of the drug is determined by its absorption, distribution, metabolism and elimination from the body ("ADME" properties; Figure 1). Absorption refers to the process by which the drug moves into the blood from the site of administration. This process is usually passive, but may be carrier-mediated. Distribution refers to the dissemination of the drug in the body, and is governed by blood flow and the ability of the drug to enter cells. This may be mediated by protein carriers in blood. Oral medications are absorbed by the gastrointestinal tract and delivered to the liver through the hepatic portal system, where they may be subject to metabolism by the liver. Metabolism refers to the process by which drugs are structurally altered by cellular enzymes to either activate or inactivate them. Many drugs are delivered as inert "prodrugs" to facilitate their solubility for absorbtion and distribution, to later be metabolized into their active form. Other modifications may inactivate the drug or modify it to promote clearance. Excretion refers to the process by which the drug is eliminated from the body. Drugs may be excreted in their active form or after metabolism, and may leave via urine or bile.

The onset, peak and duration of drug activity depends on all of these mechanisms, which may operate with greater or lesser efficiency depending on the drug, the age or gender of the individual, ethnicity, pregnanacy or variation in various enzymes or transporter proteins.

Consider as an illustration simvastatin (sold as Zocor), one of the most common cardiovascular drugs to treat dyslipidemia and to manage patients at risk for cardiovascular disease. Simvastatin is an inhibitor of HMG Co-A reductase, the rate-limiting enzyme in endogenous cholesterol biosynthesis. The effective dose of active simvastatin in a patient is a function not only of dosage, but of metabolism:

- Organic Anion Transporting Polypeptide 1B1 (OATP1B1) is expressed mainly on the sinusoidal membranes of human hepatocytes and mediates influx of substrates from blood into the hepatocytes. A specific variant form of OATP1B1 results in doubling of the plasma concentrations of active simvastatin, increasing the risk of simvastatin-induced myopathy and potentially impairing its cholesterol-lowering action.[4]
- Simvastatin is taken orally as a prodrug, an inactive lactone that must be hydrolyzed in the liver to produce the active agent, simvastatin acid. Oxidative metabolism of simvastatin lactone in the liver is catalyzed by cytochrome P450 3A4 (CYP3A4) with contributions from CYP3A5, CYP2C8 and UDP-glucuronosyltransferase.[5-7] Inhibition of CYP3A4 by drugs such as itraconazole, verapamil or erythromycin, or by ingestion of grapefruit juice, significantly elevates simvastatin and simvastatin acid concentrations in plasma, again with potentially pathological consequences.[8-10]

Table 1 summarizes examples of medicines that interact with CYP3A4 to inhibit or induce simvastatin activity. With this illustration, it is clear that the efficacy of a drug in a given patient can vary depending on the variants at several or many genes, as well as drug-drug and drug-dietary interactions.

Table 1: Examples of medicines that affect simvastin metabolism through CYP3A4

Interacting medicines	Simvastatin recommendation
Potent CYP3A4 Inhibitors	
Macrolide Antibiotics	
Erythromycin	
Clarithromycin	
Azole Antifungals	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	Combination contraindicated
Protease Inhibitors	
Ritonavir	
Telaprevir	
Boceprevir	
Gemfibrozil	
Ciclosporin	
Danazol	
Moderate CYP3A4 Inhibitors	
Amiodarone	
Amlodipine	
Verapamil	Do not exceed 20 mg/day
Diltiazem	
Nicotinic Acid (>1 g/day)	
Minor CYP3A4 Inhibitors	
Azithromycin	Case reports of rhabdomyolysis. Use with caution and monitor
Roxithromycin	
CYP3A4 Inducers	
Carbamazepine	
Phenytoin	Probable reduction in concentration. Monitor lipid profile
Rifampicin	
St. John's Wort	

Modified from: http://www.medsafe.govt.nz/profs/PUArticles/March2014StatinsAndCYPInteractions.htm

Genetics, Genomics and Inherited Variation in Drug Responses

Twin studies provide strong evidence for a genetic basis for much of the variability in drug metabolism. Briefly, monozygotic twin pairs ("identical twins") are genetically identical, whereas dizygotic twin pairs ("non-identical twins") share only half of the same alleles for each gene, like any full siblings. But unlike singleton siblings, dizygotic twin pairs share the same birth rank, maternal age and generally more similar rearing environments. Thus, greater variation in drug metabolism in dizygotic compared to monozygotic twin pairs is taken as evidence for underlying genetic factors.

Twin studies to measure drug metabolism variability for nearly a dozen different drugs and in four different countries from the late 1960s through the 1970s found that for most drugs, variation in response between monozygotic twin pairs was virtually nil, while variation between dizygotic twin pairs was more similar to the general population.[11] In several cases, pedigree studies point to a mono- or polygenic basis for variation, although the identities of the specific genes and alleles weren't determined. It is likely that the variability in response to specific drugs has a polygenic inputs, even where a single variant provides much of the predictive power.

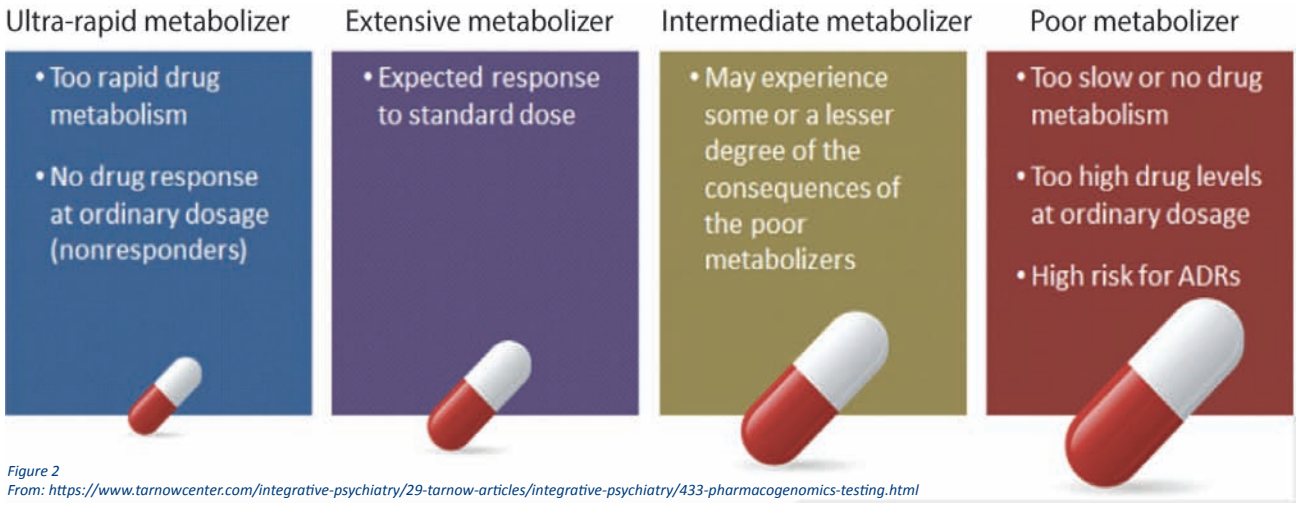

Figure 2
From: https://www.tarnowcenter.com/integrative-psychiatry/29-tarnow-articles/integrative-psychiatry/433-pharmacogenomics-testing.html

The advent of molecular genetics has identified key genetic factors underlying this variability. These factors include ion channels, receptors and, importantly, a family of enzymes that metabolize drugs on their way to the bloodstream, the cytochrome P450 enzymes.

The Cytochrome P450 Gene Family and Drug Metabolism

The human genome encodes 57 cytochrome P450 (CYP450) genes. The products of these genes are heme-containing protein enzymes, most of which are expressed in the liver. The reaction catalyzed by CYP450 enzymes is the oxidation of diverse substrate molecules. Ninety percent of drugs are metabolized by a few members of the CYP450 superfamily: CYP1A2, CYTP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5.[12] Cytochrome P450 3A4 (CYP3A4) is found in the cells lining the small intestine and colon and in the liver, and is implicated in the bioinactivation of about half of all drugs.[13]

The therapeutic efficacy of most drugs, as discussed above, is dictated by the steady-state level of active drug in circulation, which usually depends on how efficiently these compounds are metabolized as substrates of one or more CYP450 enzymes. Accordingly, variants of key CYP450 enzymes that alter catalytic activity can have a significant impact on effective dosing. Variants that lower activity can result in effective blood concentrations of drugs that may be toxic. Variants that increase activity can depress effective blood concentrations of drugs below the level of therapeutic benefit. Individuals carrying specific variants are binned into four categories of drug metabolizers: ultrarapid, extensive, intermediate and poor (Figure 2).

Table 2 summarizes a few examples of therapy recommendations based on CYP450 metabolizer status. The anticoagulant drug warfarin, for example, is used to treat thrombotic disorders but is notoriously problematic for effective dose regulation. Either excessive bleeding or excessive clotting can result if serum levels stray outside the target range. Warfarin is a substrate for the cytochromes CYP1A1, CYP1A2, CYP2C9 and CYP3A4.[14] Would patients benefit from testing for cytochrome genotype before initiating warfarin? The results of clinical studies have been somewhat mixed, but the Clinical Pharmacogenetics Implementation Consortium and the FDA have endorsed cytochrome P450 genotype-based warfarin dosing.[15] As sequencing costs continue to plummet, and additional variant associations are validated, the application of pharmacogenomics to warfarin dosing should become standard clinical practice. Examples of drugs for which pharmacogenomics testing has clinical significance are listed in Table 3.

Pharmacogenetics and Opioid Dependency

Opioid abuse has reached epidemic proportion in the U.S. Over 11 million Americans misused prescription opioids in 2016, and the number of

Table 2. Examples of drugs for which pharmacogenomics testing has clinical significance

drug class	drug	gene with clinically important variants
anticoagulant	Warfarin	CYP2C19 (cytochrome P450) VKORC1 (vitamin K epoxide reductase)
antineoplastic	Irinotecan	UTG1A1 (UDP-glucuronosyltransferase)
	6-mercaptopurine	TPMT (thiopurine methyltransferase)
	Thiopurine, Azathioprine	TPMT (thiopurine methyltransferase)
	Tamoxifen	CYP2D6 (cytochrome P450)
antidepressants	Amitriptyline/nortriptyline	CYP2C19/CYP2D6 (cytochrome P450)
	Nortriptyline	CYP2D6 (cytochrome P450)
	Coxepin	CYP2D6 (cytochrome P450)
	Paroxetine	CYP2D6 (cytochrome P450)
	Sertraline	CYP2C19 (cytochrome P450)
narcotic analgesic	Codeine	CYP2D6 (cytochrome P450)
	Tramadol	CYP2D6 (cytochrome P450)
immunosuppressant	Tacrolimus	CYP3A5 (cytochrome P450)

Modified from: https://www.slideshare.net/NarjesSadr/pharmacogenomics-50413003

opioid-related deaths increased more than four-fold since 1999.[16] 64% of the public reports having been prescribed an opioid for pain, and estimates for the rate of addiction among those taking prescription opioids for chronic pain range as high as 23%.[17]

Twin studies suggest that about half of the risk for opioid addiction is genetic.[18] One approach to genome-wide mapping of risk factors for opioid dependence is genome-wide association (GWA) studies. In this approach, the combination of many different single-nucleotide variants at sites throughout the genomes are surveyed for a population to determine whether certain variants are more common in an at-risk group. Statistically significant associations implicate nearby genes in the risk mechanism. In a 2014 study, Gelernter et al.[19] tested 890,000 variants in 5,697 individuals, including subjects with opioid and/or other substance dependence and controls. Starting with a GWA approach, then refining further by additional analyses, this study uncovered statistically significant associations with four genes required in potassium signaling pathways, as well as genes implicated in calcium signaling and calcium-mediated neurotransmitter release. Subsequent studies confirm these results and expanded the list of candidate genes, including the gene encoding the μ opioid receptor itself, the primary mediator of analgesia by opioids and their therapeutic agonists.[18]

Just as the risk of opioid addiction varies between individuals, so too the response to opioid addiction therapy can differ between patients. Metabolism of methadone and buprenorphine, two of the most widely used pharmacotherapies to treat opioid use disorders, varies among individuals.[20] Both are known substrates for metabolism by cytochrome P450. However, a suite of studies over the past several years have failed to consistently indict variants in the cytochrome P450 genes in altered methadone metabolism, likely owing to small sample sizes.[20] Current correlations between alleles of other genes and methadone or buprenorphine, while intriguing, emerge from underpowered candidate gene studies and thus are not clinically actionable. Adoption of pharmacogenomics strategies, together with larger study cohorts, will likely uncover key factors predictive of individual patient experiences.

Polypharmacy and Drug Metabolism

Polypharmacy, defined as the simultaneous use of multiple drugs by a single patient for one or more conditions, can be beneficial or harmful. For example, in patients with coronary artery disease, the combination of an angiotensin converting enzyme inhibitor, a calcium channel blocker, a diuretic, a statin and an antiplatelet drug is clearly beneficial, as it reduces the risk of a vascular event by two thirds or more.[21] In this case, different drugs targeting different mechanisms converge on the same condition.

Table 3. Examples of therapy recommendations based on CYP450 status

Drug	CYP phenotype	Therapeutic recommendation	Reference
Clopidogrel (heart attack and stroke prevention)	CYP2C19		Ref. 28
	ultrarapid metabolizer or extensive metabolizer	Dose recommended by drug label	
	intermediate metabolizer or poor metabolizer	Increased risk for reduced response to clopidogrel. Alternative antiplatelet therapy recommended if no contraindication (e.g. prasugrel or ticagrelor)	
Tricyclic antidepressants	CYP2D6		Ref. 29
	ultrarapid metabolizer	Avoid TCA use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose. Therapeutic drug monitoring should be used to guide dose adjustments.	
		Dose recommended by drug label	
	extensive metabolizer	Consider a 25% reduction of recommended starting dose. Therapeutic drug monitoring should be used to guide dose adjustments. Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose. Therapeutic drug monitoring should be considered to guide dose adjustments.	
	intermediate metabolizer or poor metabolizer	Avoid TCA use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose. Therapeutic drug monitoring should be used to guide dose adjustments.	
	CYP2C19		
	ultrarapid metabolizer	Dose recommended by drug label	
		Dose recommended by drug label	
	extensive metabolizer	Avoid tertiary amine use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19 such as the secondary amines nortriptyline and desipramine. For tertiary amines, consider a 50% reduction of recommended starting dose, and use therapeutic drug monitoring to guide dose adjustments.	
	intermediate metabolizer		
	poor metabolizer		
Omeprazole (GERD, peptic ulcers, Zollinger-Ellison syndrome)	CYP2C19		Ref. 30
	ultrarapid metabolizer	Be alert to lack of response. For eradication of *H. pylori*, increase dose by 100-200%. For other conditions, consider dose increase by 100-200%. Dose recommended by drug label	
	extensive metabolizer	Dose recommended by drug label	
	intermediate metabolizer	Dose recommended by drug label	
	poor metabolizer		

Modified from: Dong et al., 2018, Ref. 15

Table 4. Examples of potentially clinically relevant CYP inhibitor-substrate pairs

Cytochrome P450 enzyme and inhibitor	substrate
CYP2C9	
Amiodarone	Warfarin
CYP2C19	
Clarithromycin	Omeprazole
Fluoxetine	Omeprazole, Rabeprazole
CYP2D6	
Fluoxetine	Metoprolol
Paroxetine	Flecainide
Perhexiline	Vetoprolol, Venlafaxine
Doxepin	Codeine
Flecainide	Metoprolol, Paroxetine, Codeine
Quinine	Amitriptyline, Codeine, Metoprolol
sertraline	Metoprolol, Risperidone
CYP3A4	
Clarithromycin	Atorvastatin
Diltiazem	Simvastain, Atorvastatin, Methadone
Verapamil	Simvastatin, Atorvastatin

Modified from Ref. 22.

On the other hand, geriatric patients are often treated for a variety of unrelated conditions, leading to problematic interactions. In a 2014 study, Kerr et al.[22] examined the prescriptions of 1045 community-dwelling elderly Australians for co-prescription of CYP450 inhibitor and corresponding substrate drugs, together with assessments for depression, quality-of-life and cognitive status. The study found a 6.2% incidence of potentially inappropriate CYP inhibitor–substrate combinations, and physical quality of life was lower in patients with potential CYP drug-drug interactions. Noteworthy, the most common CYP inhibitor–substrate pairs were the CYP3A4 substrates simvastatin or atorvastatin combined with the CYP3A4 inhibitors verapamil or diltiazem. This combination can result in increased plasma levels of the statins, increasing the risk of myopathy or rhabdomyolysis. A limitation of this study was that patients with several conditions, including psychotic symptoms, were excluded. Many antidepressants and antipsychotics are CYP2D6 inhibitors and/or substrates; thus, this study may have missed these clinically relevant CYP450 interactions. Table 4 summarizes examples of a few pairs of drugs that are either inhibitors of, or substrates for, the same CYP450 enzyme and could be co-prescribed in a clinical setting.

The area of drug-drug interactions deserves more study, but it can be anticipated that one drug can alter the ADME properties of a second drug. However, the drug-drug interactions may not be wholly predictable (or predictable for a fraction of drugs) based on genomic information. This is because one drug may induce (or repress) gene expression of one of the members of a gene family that determines the ADME, but this dynamic change cannot be predicted from the genome sequence, and such drugs should be co-prescribed with caution.

In some cases, individual variation in drug response is due to diet, not genetics.[23] While a comprehensive review of the roles of diet and digestion in drug metabolism is beyond the scope of this review, the effect of grapefruit and certain related fruits (Seville oranges, limes and pomelos) bears remark.

For over 25 years, it has been known that grapefruit can profoundly affect drug metabolism.[24] The furanocoumarins found in grapefruit are metabolized by CYP3A4 to derivatives that bind irreversibly to the CYP3A4 enzyme, inactivating it.[25] In practice, what this means is that grapefruit consumption can dramatically increase the oral bioavailability of drugs that are dosed to be compatible with normal CYP3A4 activity, with adverse affects in some cases. Other foods that can affect drug metabolism included licorice, which can increase risk of digoxin toxicity and reduce the efficacy of diuretics and blood pressure reducing drugs, and chocolate, which in large amounts can increase the effect of Ritalin or decrease the efficacy of Ambien.

Diets can also affect the gut microbiome in a patient. There are emerging reports that demonstrate that changes to the gut microbiome alters ADME and hence efficacy of a drug. Indeed, this avenue of nascent research has been named pharmacomicrobiomics, and is an active area of discovery.[26] While changes in the gut microbiome alter efficacy and toxicity of a drug, it is not determined by the patients' genome. Therefore pharmacomicrobiomics studies are outside the scope of this review.

The Future of Pharmacogenomics

Driving progress in pharmacogenomics will be the major stakeholders:

- Patients and their physician(s) will be incented to obtain personalized pharmacogenomic data to maximize benefits and minimize risk/side effects of the drugs they consume;
- Insurers (private insurers, Medicare, Veterans Administration) will welcome pharmacogenomic data to minimize the prescription of drugs to patients who won't benefit. Precision medicine has the potential to increase efficiency of health care costs (currently over 18% of GDP);
- Drug companies will exploit pharmacogenomics data to target drug development for the largest market. They will also benefit from pharmacogenomics to avoid drug-related adverse effects that could prevent them from maximizing a return on development investment.

At the center of the clinical application of pharmacogenetics is the question of who controls the patient data. Do insurance companies, which end up having to pay for expensive drug regimens, have a right to demand genomic data to support the choice of drug and dosage before approving reimbursement? The emerging view is that there are are two kinds of data: one is the patient's data, which would belong to the patient and require patient permission to use; the second is aggregated de-identified data, which could be available without the patient's specific consent but would be given at the time the sample was obtained for sequencing.

The current state-of-the art is to use next-generation sequencing for targeted genes (panels). Current panels identify 355 variants in nearly sixty genes, and are likely to grow in the near future. These 355 variants cover about 240 FDA-approved drugs [Ref. 1; Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org/genes-drugs/)]. The goal of pharmacogenomics is to extend the benefits of precision medicine to the pharmacy. The predictive power of pharmacogenomics will continue grow exponentially, as DNA sequencing costs fall and detailed reliable risk associations continue to be uncovered. As genome sequencing continues to get cheaper, eventually everyone could have their genome sequence on a card to be assessed whenever a prescription is written. Currently, the modest amount of data connecting specific DNA sequence variants to specific effects on drug metabolism limits pharmacogenomic applications. As more variants that influence the metabolism of specific drugs are discovered, increasingly precise statistical models will be able to weight the respective contributions of these variants to drug metabolism. In this way, patient genomes can be evaluated to set optimal dosing on an individual basis. A barrier for the implementation of pharmacogenomics is the translating of genetic laboratory test results into actionable prescribing decisions. This will require education of patients, health care providers and pharmacists, as well as payers, to effectively use this tool.

Conclusion

The potential of modern pharmacy has been constrained by the fact that different patients react differently to different drugs. Presently, the clinical approach has been to prescribe the drugs that have worked for most people and wait for the outcome. In response to adverse outcomes, dosage can be tweaked or alternative compounds can be substituted. In the case of anti-tumor drugs, the time required to properly tailor chemotherapy to patient metabolism on a trial-and-error strategy could be fatal.

Pharmacogenomics offers an alternative to this ad hoc strategy. The growing understanding of genes that control metabolism of specific drugs, combined with a comprehensive genotype of each patient, offers "precision medicine" in a very literal sense.

An important caveat is that while variants in the protein-coding regions of key metabolic genes can easily be identified using current annotation data, variants that affect expression levels of genes without affecting the gene products can also have important clinical consequences, but are difficult to identify with our current knowledge.

Nevertheless, the future of pharmacogenomics is bright. As Francis Collins presciently observed: " . . . if everybody's DNA sequence is already in their medical record and it is simply a click of the mouse to find out all the information you need, then there is going to be a much lower barrier to beginning to incorporate that information into drug prescribing. . . . And it should improve outcomes and reduce adverse events."[27]

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Disclosure

None reported.

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