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REVIEW

Understanding the Essentials of Pharmacogenomics- The Potential Implications for the Future Pharmacotherapy

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ABSTRACT

The genetic makeup affects drug responses to a greater extend. Personalized medicine deals with the prescription of specific therapeutic agent best suited for an individual based on the pharmacogenetic and pharmacogenomic information. By understanding the genetic variations in an individual, it becomes easy for a clinician to select the appropriate drug in an adequate dose. Genetic variations can influence drug action in many ways, the common ones being the drug metabolizing enzyme (CYP450), the site of drug action (receptors), and at the drug transporter levels (p-glycoprotein). Safety and efficacy of many commonly prescribed drugs like aspirin, isoniazid, omeprazole, warfarin, hydralazine etc are affected by the genetic makeup of individuals. Similarly, the pharmacotherapy of common diseases like asthma, hypertension, depression etc is also influenced by genetic variations. Pharmacogenomics can also offer benefits like proper determination of drug dosage, and production of better vaccines and can definitely reduce the healthcare costs and helps to enable drug safety by understanding the genetic profile of an individual. Integration of pharmacogenomic information into clinical practice will also require clinical trials to assess their clinical usefulness. The usefulness of pharmacogenomic data also depends upon the affordability, ease of application, and ease of interpreting the results etc.

Keywords: Aspirin resistance, Human genome, Personalized medicine, Pharmacogenetics, Pharmacogenomics

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Introduction

It is well recognized that different patients respond differently to the same medication. Such differences in drug toxicity or drug efficacy are often much greater across a population of patients than between monozygotic twins. Interindividual variability in drug efficacy and toxicity is related to several factors such as age, sex, race and inherited differences in the genes that control drug disposition and effects in humans.[1] Pharmacogenomics refers to the entire spectrum of genes that determine drug safety and efficacy whereas pharmacogenetics refers to monogenetic variants that affect drug response.[2] Pharmacogenomics is a science that examines inherited variations in genes that dictate drug response and express the way these variations result in good response to a drug, a bad response to a drug, or no response at all. Pharmacogenomics holds the promise that drugs might be tailor made for individuals and adapted to each person's genetic make-up which has been termed as 'personalized medicine'. Personalized medicine means the prescription of specific therapeutic agents best suited for an individual based on pharmacogenetic and pharmacogenomic information. [3]

In this article, the authors provide an overview regarding the importance of understanding the principles of pharmacogenomics and also provide some of the clinically significant examples of variation in drug response due to the differences in the genetic make up. The authors also highlight the future benefits, barriers and ethical considerations associated with pharmacogenomics.

Pharmacogenomics principles in personalized medicine: Effective pharmacotherapy results only when the drug reaches in sufficient amount at the target site or in the systemic circulation. Many factors can influence the patients' response to drugs including gender, dietary habits, concurrent illness, concomitant drug use etc.[2] For many medications, these interindividual differences are due in part to polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and/or drug targets (e.g., receptors, enzymes)[4].

The recognition of the complexities involved in the gene and the advance of genetics into genomics led to the broader science of pharmacogenomics. This led to the vision of "personalized medicine," that is, making drug use more effective and safer by giving drugs that fit a person's genes.[5] As the initial draft of human genome has revealed, there are over 1.4 million single nucleotide polymorphisms (SNP_S) in the human genome, with over 60,000 of these residing in the coding regions of human genes.[1]

Some of these SNP_S have already been identified to affect metabolism or effects of drugs. For example, genes encoding cytochrome P450 enzymes, N-acetyl transferase etc. Genetic make up is thus one of the commonest factors affecting the drug response. These variations in the genetic make up of an individual can change the manner in which the patient responds to the drug. Adverse Drug Reactions (ADRs) are estimated to be one of the top ten causes of death and up to 50% of adverse reactions are possibly related to the genetic makeup of the susceptible individuals.[6] By understanding the variations in the genetic makeup of an individual, it becomes easy for a clinician to select the appropriate drug at the appropriate dose.

Genetic variations and drug response: The variations may be at the drug metabolizing enzyme (CYP450), at the site of drug action (receptors), or at the drug transporter levels (p-glycoprotein). The outcome of these variations may be lack of or decreased therapeutic efficacy or an increased risk of toxicity.

Genetic variations in genes of drug metabolizing enzymes (P450 genes): The cytochrome P450 system is a group of enzymes that are responsible for metabolizing many endogenous and exogenous substances,[7] including 40% to 50% [8] of all medications into more hydrophilic substances. There are approximately 50 CYP450 genes. Despite this multiplicity, the bulk of drug metabolism is carried out by a small number of P450 enzymes found in families 1, 2 and 3. [9] The predominant drug metabolizing P450s and their genetic variability is listed in Table/Fig 1.

Genetic variations in genes of drug transporters: P-glycoprotein, a drug transport proteins exhibits genetic polymorphism. P-glycoprotein is an energy dependent transmembrane efflux pump encoded by the multidrug resistance-1 (MDR-1) gene. This transport molecule uses the energy of ATP to expel drugs from the cell. P-glycoprotein is widely distributed on normal cell types including intestinal enterocytes, hepatocytes, renal proximal tubules, and endothelial cells lining the blood-brain barrier. P-glycoprotein affects the distribution of cancer chemotherapeutic drugs, digoxin, cyclosporine, tacrolimus, protease inhibitors etc. Increased intestinal expression of P-glycoprotein can limit the absorption of P-glycoprotein substrates, thus reducing their bioavailability and preventing attainment of therapeutic plasma concentrations. Conversely, decreased P-glycoprotein expressions may result in supratherapeutic plasma concentrations of relevant drugs and drug toxicity. Other examples of polymorphic drug transporter proteins include the dipeptide transporter, organic anion and cation transporters, and L-amino acid transporter. Their effects on drug distribution are the focus of ongoing research.[17], [18].

Table/Fig 1: The predominant drug metabolizing P450s and their genetic variability

Cytochrome P450 type	Genetic variability
CYP1A	• It is involved in the metabolism of many drugs like theophylline, caffeine, tacrine etc.[10]
CYP2A6	• It is important for metabolism of coumarin and nicotine.[11] Three defective CYP2A6 alleles have been identified which result in an absence of CYP2A6.[12] There is a likely relationship between defective CYP2A6, nicotine metabolism, smoking behavior, and cigarette consumption.[13]
CYP2D6	• A recent clinical utility of CYP2D6 polymorphism is resurgence of perhexilline as prophylactic antianginal agent in Australia.[14] This drug was originally discarded due to hepatotoxicity and nephrotoxicity. It is now established that perhexiline toxicity is prevalent in CYP2D6 poor metabolizer phenotype and safe use of this drug can be achieved by performing CYP2D6 genotyping.[15]
CYP2E1	• It is important for metabolism of paracetamol and many carcinogens. It is also induced following exposure to alcohol. Only one variant of CYP2E1 gene has been identified and has been linked with altered susceptibility to many chemically induced cancers.[16]
CYP3A4	• The human CYP3A subfamily comprises two genes expressed in adults, CYP3A4 and CYP3A5 and a third gene expressed in fetal life CYP3A7.[9] It is the most important drug metabolizing enzyme responsible for metabolism of around 60% of current drugs. CYP3A4 activity may be increased by different drugs like rifampicin, phenobarbital and steroids.

Genetic variations in genes of drug targets: Genetic polymorphisms occur commonly for drug target proteins including receptors, enzymes, and intracellular signaling proteins. Some of the drug targets that exhibit genetic polymorphism are the beta-1 receptor, beta-2 receptor, dopamine-2 receptor, dopamine-3

receptor, estrogen receptor etc. Based on the type of polymorphisms exhibited, the response of the drugs varies. There may be increased side effects or lack of therapeutic efficacy. [17]

Clinical applications of pharmacogenomics: The inherent variations in the genetic makeup of an individual can result in considerable difference in the drug response. Some of the clinically important examples of variation in drug response due to the difference in the genetic makeup are listed in Table/Fig 2.

Technology to assess gene polymorphism:[36], [37], [38], [39], [40]
DNA microarrays, are one of the oldest methods used in assessing the human genetic makeup. The common elements of this approach to nucleic acid analysis are an immobilized or tethered nucleic acid (DNA or RNA) species that is hybridized with a second, solution-phase DNA or RNA species that is generally labeled with a detectable molecule such as a fluorescent dye.

These days Lab card or lab-on-a-chip devices are becoming increasingly important in genomic analysis. Polymerase chain reactions, sequencing reactions, primer extension reactions, and nuclease cleavage reactions carried out in these devices realize an order of magnitude improvement in throughput and economy over microtitre plate- based biochemistry. Increasingly simple and inexpensive genetic testing systems based on high-throughput DNA microarrays and microfluidic devices should eventually allow patients to be prescreened for specific, relevant polymorphisms before drug therapy is initiated.
We can determine simultaneously many thousands of polymorphisms in a patient. The French genomics company, Genset, currently uses gene chips with 60 000 single nucleotide polymorphism markers sufficient for a complete genomic scan applied to clinical drug trials in partnership with major pharmaceutical companies.

Table/Fig 2: Clinical applications of pharmacogenomics

Conditions	Comments
Thiopurine methyltransferase (TPMT) gene variations	• TPMT plays a role in chemotherapy of childhood leukemias by breaking down thiopurine drugs.[19] Patients with TPMT deficiency are more susceptible to life-threatening myelosuppression upon initiation with thioguanine and may require a large dose reduction.[20]
Aspirin resistance	• Aspirin resistance may be a cause of recurrent vascular events in patients taking aspirin. Amongst the several causes attributed to aspirin resistance are genetic polymorphisms involving platelet glycoprotein Ia/IIa, Ib/V/IX, and IIb/IIIa receptors, and collagen and vonWillebrand factor receptors, polymorphism of cyclooxygenase-1, thromboxane A2-synthetase etc. [21]
Pharmacotherapy of depression	• All Selective Serotonin Reuptake Inhibitors (SSRIs) are metabolized in the liver by various CYP450 isoenzymes, including CYP2D6, CYP1A2, CYP3A4 and CYP2C19.[22] For example, polymorphic CYP2C19 isoenzyme plays a major role in N-demethylation of sertraline and fluoxetine and both extensive and poor metabolizers have marked differences in disposition of both drugs.[23]
Acetylation of isoniazid	• Isoniazid is acetylated in the liver and the rate of acetylation is genetically determined as slow or fast acetylation. Slow acetylators have higher serum levels of isoniazid than rapid acetylators. This is of little significance in terms of efficacy, with the exception of a once weekly dosing regimen, wherein rapid acetylators have a poorer response than slow acetylators.[24], [25]. Peripheral neuropathy, one of the most common side effect of isoniazid occurs most often in slow acetylators.
Omeprazole metabolism	• A major enzyme involved in the metabolism of omeprazole is the polymorphically expressed cytochrome P450 (CYP) isoform S-mephenytoin hydroxylase also known as CYP2C19. Some patients who are deficient in this enzyme system will be slow metabolizers of omeprazole. Slow metabolizers can produce plasma concentrations five times or more high than patients with normal metabolizing enzyme system.[26]
Warfarin metabolism	• Warfarin is metabolized principally by the CYP2C9 enzyme. Patients with variant forms of the CYP2C9 enzyme (including CYP2C9*2 and CYP2C9*3 alleles) may be at increased risk of over-anticoagulation and bleeding events. Those with a variant genotype has an increased risk of an above-target international normalized ratio (INR), a longer adjustment time to achieve a stable warfarin dose, and a higher risk of bleeding events.[27]
Hemolytic reactions due to primaquine	• Primaquine causes hemolytic anemia glucose-6-phosphate dehydrogenase (G6PD) deficiency patients. The severity of hemolysis is dependent on the dose of the drug, the degree of enzyme deficiency, and other factors that can increase hemolysis (other drugs, liver disease, infection).[28], [29].
Lack of analgesic effect with codeine	• Patients with multiple CYP2D6 gene copies metabolize codeine more rapidly (ultra-rapid metabolism), whereas patients who lack functional CYP2D6 genes do not metabolize codeine to morphine and do not experience analgesic effects. Multiple CYP2D6 gene copies occur in 4 to 5% of the United States population and up to 29% of the population of Ethiopia and Saudi Arabia.[8]
Safety and efficacy of hydralazine	• In one study, rapid acetylators of hydralazine required an approximately 60% larger dose of hydralazine than slow acetylators for adequate blood pressure reduction.[31] Approximately 50% to 65% of Caucasians, Blacks, South Indians and Mexicans are slow acetylators, while 80% to 95% of Eskimos, Japanese, and Chinese are rapid acetylators.[32]
Pharmacotherapy of hypertension	• To date, more than forty studies have investigated associations between genetic polymorphisms and response to antihypertensive drugs. Angiotensin-converting enzyme (ACE) inhibitors and beta blockers have been most frequently studied, followed by angiotensin II blockers, diuretics, adrenergic alpha-agonists, and calcium channel blockers. In total, 160 possible gene polymorphism-drug interactions have been explored, with about one-quarter of these showing that genes predict drug response.[33]
Asthma	• Responses to the three major classes of asthma therapy, beta-agonists, leukotriene

	antagonists and inhaled corticosteroids, demonstrate wide inter-individual variability. Moreover, both asthma and the traits measured in response to asthma therapy, including forced expiratory volume at 1 second (FEV_1), are highly heritable. This indicates that genetics may play a prominent role in the determination of the therapeutic response to asthma.[34] • One population-based study identified that non-synonymous SNPs of ADRB2 at codons 16 and 27 is significantly associated with bronchodilating response to inhaled short acting beta-agonists.[35]

Future benefits of pharmagenomics: [41-43] Pharmacogenomics is a growing field of science and offers many advantages. Some of the future benefits of pharmacogenomics are mentioned below.

Better and safer drugs: It will be possible to analyze patient's genetic make-up and prescribe the drug with the best response, therefore increasing safety and minimizing ADRs. In the United States alone, pharmacogenomics can reduce the 100,000 deaths and 2 million hospitalizations that occur each year due to ADRs.

Table/Fig 3: Barriers to the process of pharmacogenomics

Barriers	Comments
Complexities of finding gene variations that affect drug response	• SNP_S occur at every 100 to 300 bases along the 300 billion base human genome. Therefore, millions of SNPs must be identified and analyzed to determine their involvement, if any, in drug response. Since many genes are likely to influence drug response, obtaining a bigger picture on the impact of gene variations on drug responses is highly time consuming and complicated.
Limited drug alternatives	• In many cases only one or two drugs may be available for treatment of a particular condition. If gene variations exclude use of these drugs, patients may be left without any alternatives for treatment.
Disincentives for drug companies to make multiple pharmacogenomic products	• Since it costs hundreds of millions of dollars to bring a drug to the market, it is questionable whether pharmaceutical companies will be interested in developing drugs that serve only a small portion of population
Educating healthcare providers	• Introducing multiple pharmacogenomic products to treat the same condition for different population subsets undoubtedly will complicate the process of prescribing and dispensing drugs. Physicians must execute an extra diagnostic step to determine which drug is best suited to each patient. To interpret the diagnostic accurately and recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics.

Drug development and testing: Pharmaceutical companies could exclude from clinical trials those people whose pharmacogenomic screening indicates that the drug under evaluation will be ineffective or harmful. It will increase the chance of the drug making it into the market. Clinical trials may become safer, smaller, faster and less expensive, ultimately reducing drug costs.

Determination of drug dosage: Pharmacogenomics will replace dosage based on age and weight to a dosage determined by efficacy and metabolism of the drug in the body.

Better vaccines: Better vaccines can be made of genetic materials, either Deoxy Ribo Nucleic Acid (DNA) or Ribo Nucleic Acid (RNA). Along with all the benefits of existing vaccines and minimum risk, they will be inexpensive, stable, and easy to store. They will activate the immune system but be unable to cause infections.

Advanced screening for disease: Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of susceptibility to a particular disease will allow

careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapeutic effect.

Decrease in overall cost of health care: Decreased number of failed trials, small and fast clinical trials, decreased number of ADRs, and increase in the range of possible drug targets will ultimately result in decrease in the overall cost of health care.

Barriers to pharmacogenomics progress: [44] Pharmacogenomics is a developing research field which is still in infancy. Several obstacles have to be overcome before the benefits of pharmacogenomics can be realized. Some of the important barriers to pharmacogenomics are listed in Table/Fig 3.

Ethical considerations associated with pharmacogenetics: Pharmacogenetics offers the prospect of an era of safer and more effective drugs, as well as individualized use of drug therapies. The effect of human genetic variance on responses to therapy will influence drug-development clinical trials and the use of products in clinical practice. It also promises to raise new ethical challenges, particularly in the fields of research and therapy. [45]

In general genetic testing can have profound legal, ethical and social implications. For example, knowledge that a patient is at risk for developing a genetic disorder could result in discrimination by employers or insurance companies. In additional, this information may cause emotional distress for the individual at risk and his or her family members. However, within the context of pharmacogenetics, testing involves the search of genetic variation linked to drug efficacy or toxicity rather than to disease susceptibility. This form of testing carries little legal, ethical and social concerns. [17]

It becomes very important that, the ethical issues arising in research and clinical application of pharmacogenetic technologies be addressed before realizing the benefits of pharmacogenetics. These can be addressed under six headings: regulatory oversight, confidentiality and privacy, informed consent, availability of drugs, access, and clinicians' changing responsibilities in the era of pharmacogenetic medicine. [46]

Integration of pharmacogenomic information into clinical practice will also require clinical trials to assess their clinical usefulness, including the impact of tests on therapeutic outcomes. Trials will also be needed to demonstrate the effectiveness of education and counseling. [47]

Pharmacogenomic data submission during drug development: In order to address the issues related to pharmacogenomics, the United States Food and Drug Administration (US FDA) in November 2003 issued a new document "Draft Guidance for Industry: Pharmacogenomic Data Submissions" that encourages drug and biologicals developers to conduct pharmacogenomic tests during drug development and clarifies how US FDA will evaluate the resulting data. In the draft guidance, US FDA said that the promise of pharmacogenomics lies in its potential ability to individualize therapy by predicting which individuals have a greater chance of benefit or risk, thus helping to maximize the effectiveness and safety of drugs.. Using genomic testing to guide drug therapy will constitute a significant shift from the current practice of population-based treatment towards "fine-tuning" individual therapy. [48] In developing countries, the system of pharmacogenomic data submission during drug development is still in its infancy.

Conclusion

Many prescribed drugs either don't produce the desired therapeutic effect or have extensive undesired effects. Since pharmacogenomics is linked to drug efficacy as well as drug toxicity, it would be desirous to have genetic screening while prescribing those drugs that are affected by the human genetic makeup. Prescribing drugs to the patients based on their genetic makeup will certainly improve the quality of health care and also reduce overall cost by decreasing the number of treatment failures and adverse drug reactions. The day is not far away when a clinician changes his/her decision about a drug considered for the patient because the patient's genetic test indicate that he/she could suffer serious adverse effects to the medication. Pharmacogenomics will also transform the way the clinical trials are conducted by allowing for the selection of a more homogeneous study population, there by reducing the size and cost of clinical investigation. However, factors such as affordability, ease of application, and ease of interpreting the results

play a vital role in extrapolating the pharmacogenomic data to personalized medicine.

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