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Pharmaceutical Sciences **REVIEW ARTICLE ……!!!**

PHARMACOGENOMICS AND PERSONALISED MEDICATION THERAPY: AN OVERVIEW

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KEYWORDS:

Genomics, drug interaction, genes, optimal therapeutic response, toxicity, personalized medication therapy.

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ABSTRACT

The rise in advancement in the Medical and Pharmaceutical sciences has given rise to a new branch of science which deals with the study of genes in a whole genomics with drug interaction. The study tells about how a drug's activity gets influenced by the genes. It helps to understand why some individuals respond to drugs and others do not, why some individuals require higher or lower doses to achieve an optimal therapeutic response, and tries to help the physician identify those patients who will respond favourably to therapy or develop side effects. According to some latest surveys it has been found that billions of people worldwide are dying due wrong medication or due to harsh toxicity of medicines. Due to the inappropriate medication therapy the patient's hospital stay duration are also increasing which in turn increases the total healthcare cost. In this article, we have discussed how a gene can affect the drug activity, how pharmacogenomics can be utilised as personalised medication therapy and how it will help in reduced healthcare cost in future.

INTRODUCTION:

Pharmacogenomics is a newer branch of pharmacological sciences which helps in studying the relationship between genetic predisposition of an individual and his ability to metabolize a drug. There are often large differences among individuals in the way they respond to medications, whether the endpoint is host toxicity, treatment efficacy, or both. Potential causes for variability in drug effects include the nature and severity of the disease being treated, the individual's age and race, organ function, therapy, drug interactions, and illnesses. Although these factors are often important, inherited differences in the metabolism and disposition of drugs, and genetic polymorphisms in the targets of drug therapy (e.g., receptors), can have an even greater influence on the efficacy and toxicity of medications. Some clinical observations of inherited differences in drug effects were first documented in the 1950s (1, 2, 6), giving rise to the field of pharmacogenetics, which has now been rediscovered by the pharmaceutical industry and a broader spectrum of academia, giving birth to pharmacogenomics. Although the two terms are often used interchangeably, pharmacogenomics is used here to describe a genome wise approach to identify the network of genes that govern an individual's response to drug therapy. The ultimate goal of pharmacogenomics is to define the contributions of genetic differences in drug disposition or drug targets to drug response, thereby to improve the safety and efficacy of drug therapy through use of genetically guided, individualized treatment. With more sophisticated molecular tools available for detection of gene polymorphisms, advances in bioinformatics and functional genomics, and the wealth of new data emerging from the human genome projects, the genetic determinants of drug disposition and effects are being rapidly elucidated, and these data are already being translated into more rational drug therapy (7, 12, 14).

The study of the molecular genetic basis for inherited differences in drug metabolism began in the late 1980s, with the initial cloning of a polymorphic human gene encoding the drug metabolizing enzyme debrisoquin hydroxylase (CYP2D6) (18). The human genes involved in many such pharmacogenetic traits have been now isolated, their molecular mechanisms studied, and their clinical importance are more clearly defined and highlighted in this article. The inherited differences in individual drug metabolizing enzymes are typically monogenic traits, and their influence on the pharmacokinetics and pharmacologic effects of medications is determined by the importance of these polymorphic enzymes for the activation or inactivation of drug substrates. The effects ranges from profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (e.g., azathioprine, fluorouracil) (15) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (e.g., codeine) (10). Alternatively, for drugs that have a very

wide range of therapeutic index (e.g., metoprolol), the altered pharmacokinetics in CYP2D6-deficient individuals translates into clinically unimportant changes in drug effects.

However, the overall pharmacologic effects of medications are more often polygenic traits, determined by numerous genes encoding proteins involved in multiple pathways of drug metabolism, disposition, and effects. Such polygenic traits are more difficult to verify in clinical studies, especially when a medication's metabolic fate and mechanism of action are poorly defined. However, as the molecular mechanisms of pharmacologic effects, genetic determinants of disease pathogenesis, and polymorphisms in genes that governs the drug metabolism and disposition are clarified, these genetic determinants become more significant.

Furthermore, the human genome project, combined with functional genomics, bioinformatics, and high-throughput screening methods, is providing powerful tools for studying polygenic determinants of disease pathogenesis and drug response.

Elucidating Therapeutic Decisions and Predicting Drug Efficacy

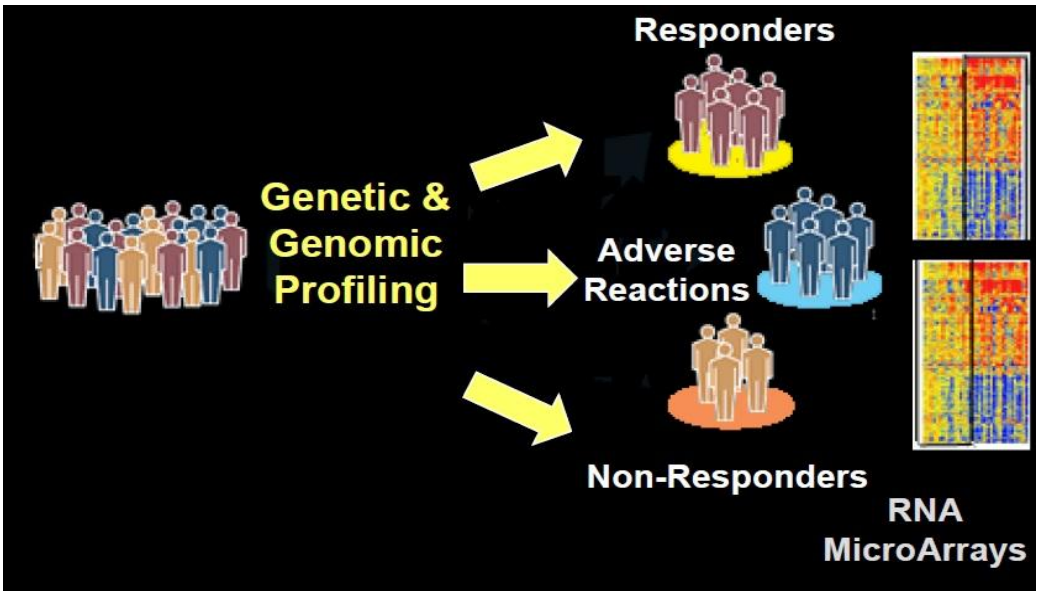

Figure-1

Efficacy of Various Drugs

Class of Drugs	% Insufficient Response
β-Blockers (Cardiac)	15-25
β 2-Agonists (Bronchodilators)	40-70
ACE Inhibitors (Hypertension, Proteinuria)	10-30
Selective Serotonin Reuptake Inhibitors (Depression)	10-25
HMG-CoA Reductase Inhibitors (Stanins)	30-70
Tricyclic Anti-Depressants (depression)	20-25

Table-1

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The below diagrammatic representation shows how genes are involved in determining drug efficacy:

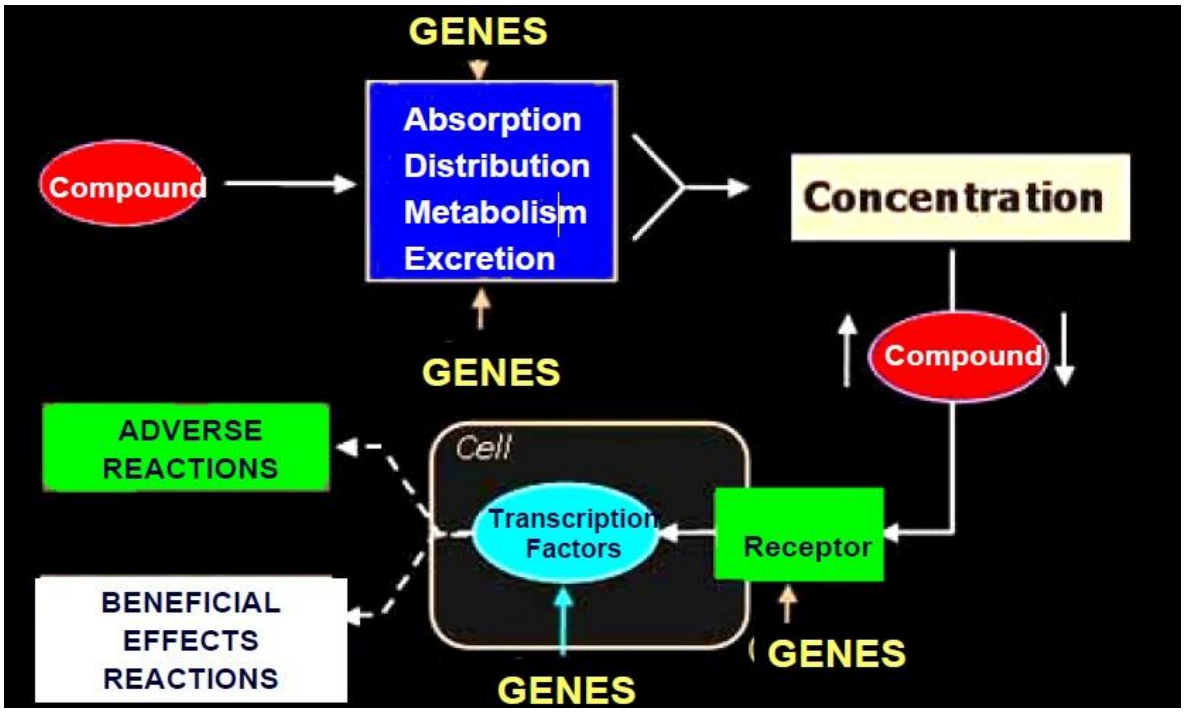

Figure-2

The mechanisms of genetic variations

The genetic variations are the results of multiple mechanisms such as insertion, deletion, variable tandem repeats and microsatellites but the most frequent polymorphisms are point mutations or single nucleotide polymorphisms (SNPs), accounting for over 90%. Some of the polymorphisms are without consequences, but others cause altered protein, truncated protein, unstable protein or protein due to expression level. A polymorphism means a mutation in the genetic code that occurs in more than 1% of a population.

Pharmacogenetic profiles

There are two approaches of creating genetic profiles for enabling optimal treatment. The first approach refers to a making of specific hypothesis on the genes that causes therapeutic response modification and their testing in all individuals irrespective of their therapeutic response (gene candidates).

The second approach implies the search for so-called SNP profile (SNP prints) related with efficient or adverse events in a respective population (forensic precision). This is known as the pharmacogenetic approach, i.e. search for SNP profile. According to literature data produced by the experts in the field of pharmacogenetics, for clinical use preference is given to the search for SNP profile in individuals by whole genome scanning. Examples of specific genes modifying drug

response, and which could be currently used in clinical practice are the genes encoding for drug metabolizing enzymes from the families CYP450, CYP2D6, 2C19 and 2C9, then phase II enzymes NAT2 and TPMT, B2-AR receptors, and some enzymes involved in the metabolism of antitumor drugs.

Some selected drugs whose safety and efficacy are affected by gene variations:

The table below is a partial list of drugs that exhibit reduced therapeutic effectiveness and/or safety concerns in patients carrying certain genetic variations. These variations often make the drug unsafe or unsuitable for patients who possess the variations. The list contains examples of drugs that are affected by inherited genetic variations and the variations that are acquired and present in tumor tissue.

Drug	Gene(s)	Drug	Gene(s)
Codeine	CYP2D6	Irinotecan (Camptosar®)	UGT1A1
Atomoxetine (Strattera®)	CYP2D6	Abacavir (Ziagen®)	HLA-B*5701
Clopidogrel (Plavix®)	CYP2C19	Carbamazepine (Tegretol®)	HLA-B*1502
Tamoxifen (Nolvadex®)	CYP2D6	Trastuzumab (Herceptin®)*	Her2/neu
Warfarin (Coumadin®)	CYP2C9, VKORC1	Panitumumab (Vectibix®)*	KRAS
Azathiopurine (Imuran®)	TPMT	Imatinibmesylate (Gleevec®)*	C-KIT

Table-2

* The response to these drugs is dependent on genetic variations that are present in tumour tissue.

Adapted from U.S. Food and Drug Administration website (www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)Accessed September 5, 2015.

Metabolizer phenotype

The metabolizer phenotype describes the patient's ability to metabolize certain drugs and is based on the number and type of functional alleles of certain genes that a patient carries. These genes most commonly encode the CYP enzymes. The metabolizer phenotype can range from "poor," used to describe patients with little or no functional activity of a selected CYP enzyme, to "ultra-rapid,"

used to describe patients with substantially increased activity of a selected CYP enzyme. Depending on the type of *CYP* variation present, the patient's metabolizer phenotype and the type of drug (active pharmacologic agent or inactive prodrug precursor), therapeutic drug response is often suboptimal. The table on the following page summarizes the effects of *CYP* variation on therapeutic efficacy. (3) For example, poor metabolizers are unable to metabolize certain drugs efficiently, resulting in a potentially toxic build-up of an active drug or the lack of conversion of a prodrug into an active metabolite. In contrast, in ultra-rapid metabolizers, an active drug is inactivated quickly, leading to a sub therapeutic response, while a prodrug is quickly metabolized, leading to rapid onset of therapeutic effect.

Pharmacogenomics used in the clinical setting

Awareness of the influence of gene variations on patient response to certain drugs can help physicians decide which type of drug therapy may be appropriate, and identify cases in which a patient isn't responding as anticipated to a drug. The examples that follow illustrate three categories for which pharmacogenomic knowledge can help inform therapeutic decisions: predicting and preventing adverse reactions, determining the efficacy of a drug for a particular patient, and predicting the optimal drug dose.

Pharmacogenomics used to predict and prevent adverse drug reactions (ADR)

Various drugs can cause severe or life-threatening reactions in patients with variations in genes that encode proteins that metabolize or are targets of the drugs. Having the knowledge about patients' genetic variations can help physicians to avoid drugs that may cause adverse reactions.

Below is an examples of drug in this category.

Codeine

The Codeine is a prodrug with analgesic properties which is primarily converted into morphine. (7,8)The Conversion into morphine is induced by the cytochrome P450 enzyme CYP2D6. Variations that decrease the metabolic activity of CYP2D6 result in a poor analgesic response due to the reduced conversion of codeine into morphine,(5) and patients carrying such a variation are considered poor metabolizers and receive little therapeutic benefit from codeine. It is estimated that 5–10 percent of Caucasians are CYP2D6 poor metabolizers; the percentage is approximately 2–3 percent in other racial and ethnic groups.(7,8,18) Variations (such as gene duplications) can also result in increased metabolic activity of CYP2D6; these result in an enhanced analgesic response due to the rapid conversion of codeine into morphine. Patients who carry such variations are at risk for opioid toxicity, which includes moderate to severe central nervous system depression. The prevalence of the CYP2D6 ultra-rapid metabolizer phenotype has been estimated at 1–10 percent in

Caucasians, 3–5 percent in African Americans, 16–28 percent in North Africans, Ethiopians and Arabs, and up to 21 percent in Asians.

Pharmacogenomics used to predict effectiveness of a drug

Various drugs are sub therapeutic or ineffective in patients with variations in genes that encode drug-metabolizing proteins or targets of the drugs. Having the knowledge about patients' genetic variations can help physicians to select the drug therapies that will be most effective for individual patients.

Below is an example of a drug in this category.

Clopidogrel

Clopidogrel is a platelet inhibitor used in the treatment of a number of cardiovascular diseases. It is often prescribed for secondary prevention following acute coronary syndromes and for those undergoing percutaneous coronary intervention. However, despite clopidogrel treatment, up to one-quarter of patients experience a subtherapeutic antiplatelet response, resulting in a higher risk for ischemic events. (9,11)

Clopidogrel is a prodrug, its antiplatelet properties are exposed only when it is converted to an active metabolite. A cytochrome P450 enzyme, CYP2C19, mediates the conversion of clopidogrel into the active metabolite. Patients who carry certain variations in CYP2C19 are considered poor metabolizers and show reduced ability to convert clopidogrel into its active metabolite, resulting in a diminished antiplatelet effect. (19, 22) Furthermore, these patients are more likely to have an ischemic event following clopidogrel therapy. (22) Approximately 2–20 percent of patients (depending on ethnicity) are likely to carry *CYP2C19* variations. (3,20)

Pharmacogenomics and Genetic Profiling

The genetic tests which detects variations in the genes that control metabolism and response to certain drugs are commercially available. Costs and insurance coverage are variable, depending on the type of test ordered. Hospital and reference laboratories as well as clinical geneticists are valuable sources of information on the best test to order and interpretation of results.

It is important to note that the field of pharmacogenomics is still developing, with new findings being rapidly reported. Clinical trials and other studies focusing on the benefits, risks and cost-effectiveness of using genetic information to inform drug therapy are under processing. In the meantime, physicians and health care providers should be familiar with the concept that genetic variations can cause their patients to respond unexpectedly to drug therapy, and that in some cases, it may be appropriate to use genetic test to guide therapeutic decisions.

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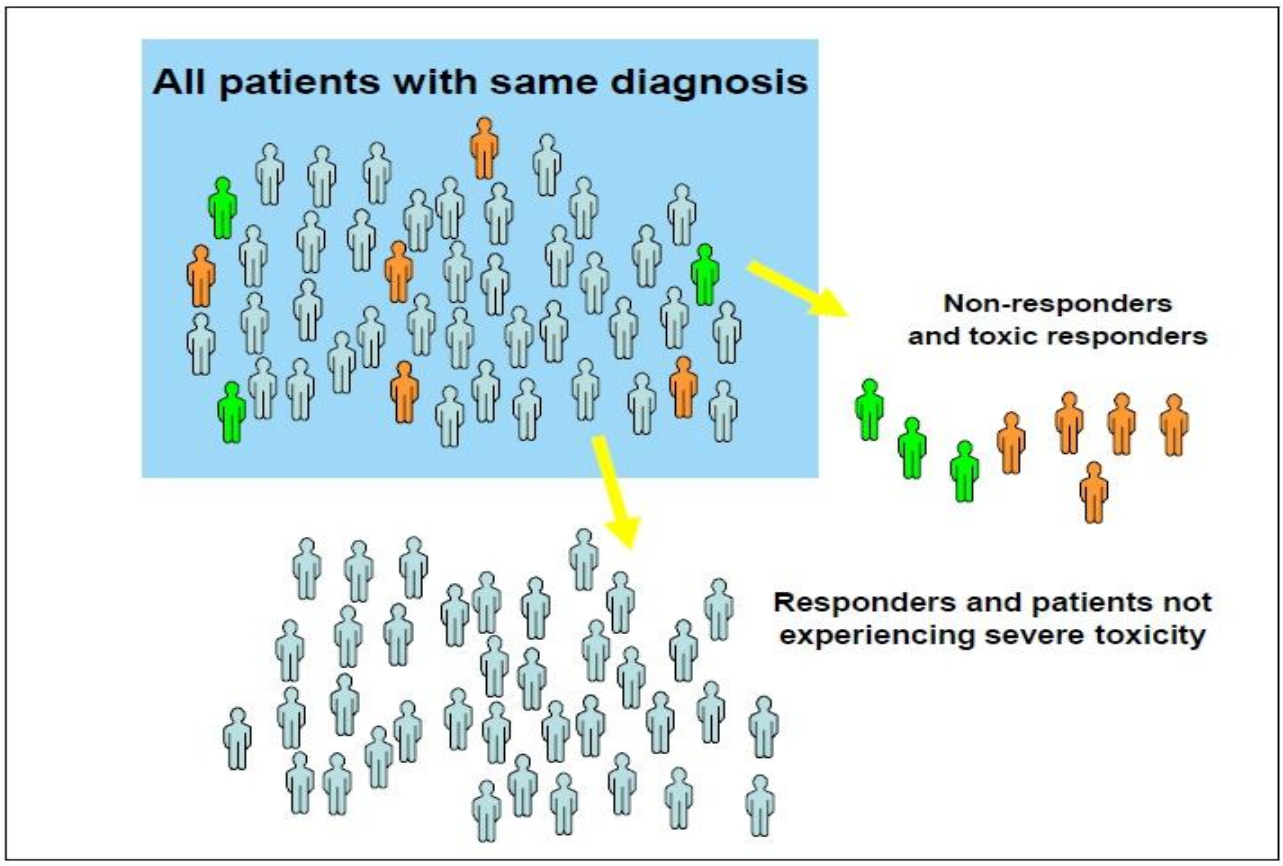

Figure-3

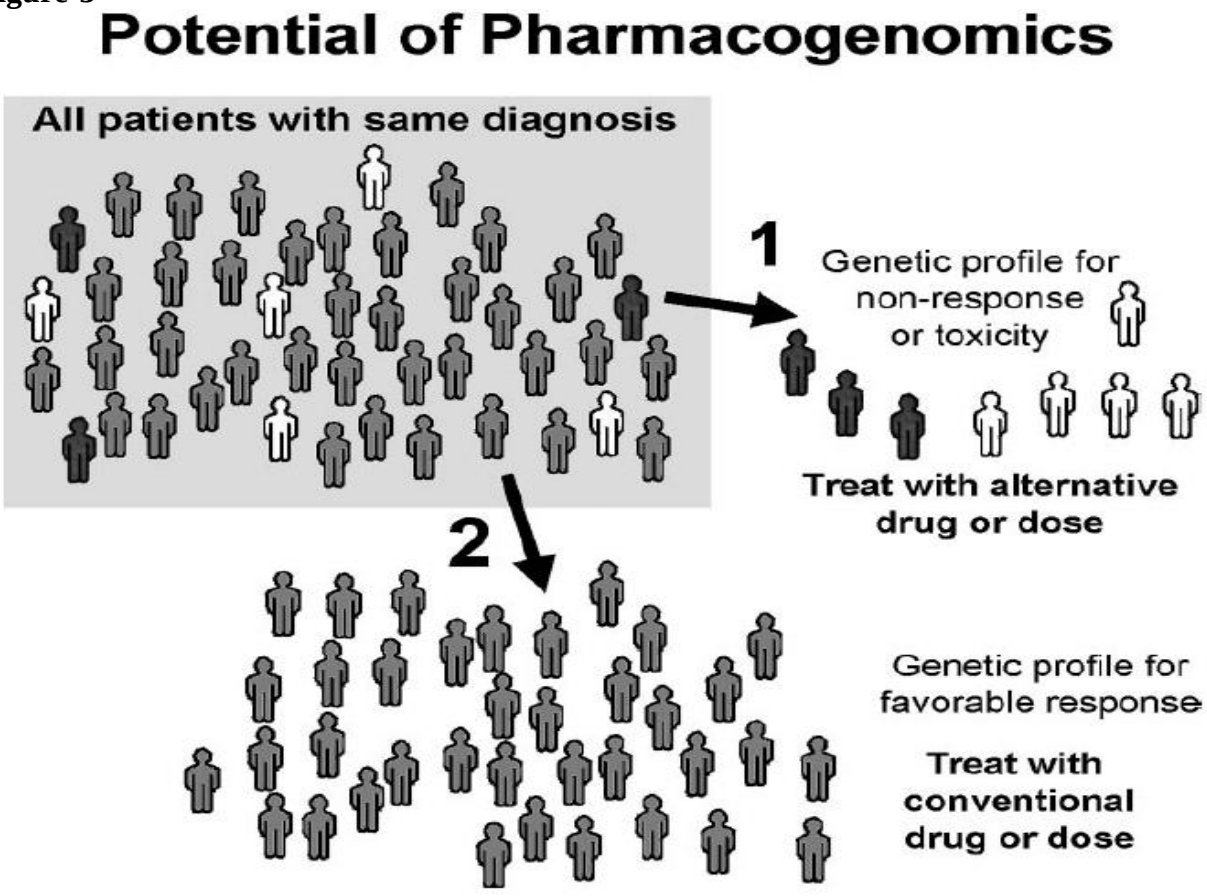

Figure-4

The potential of pharmacogenomics is to identify patients within a population with the same diagnosis (e.g., hypertension, leukemia, asthma, etc.), who are genetically predisposed either not to respond to therapy or to develop unacceptable toxicity, and then to prospectively alter their therapy to avoid treatment that is not likely to be optimal. The remaining, now more homogeneous population, can then be treated with conventional therapy in which they are not genetically predisposed to fail.

Personalised Medication Therapy

As in practical all the drug's effects to some extinct are genetically controlled, personalised medication therapy means the choice of drug for any individual will have to be determined mainly by that person's genes. This has many implications.

At the first place, in order to make any genetic test results clinically useful, they must be interpreted in terms of pharmacogenetics. The future physician will be better trained in genetics than in current phase; perhaps there will be pharmacogenetic specialists who will interpret the data for the physician; or an appropriate computer programs may be developed which will provide the necessary information to the physician. But the most effective way to introduce pharmacogenetics into clinical medicine may be a change in regulatory and industrial policies; that is, to provide information on which (if any) genes are known to affect the action of any drug to be prescribed.(23)

Secondly, a number of legal and ethical questions have to be resolved. Knowledge of a person's genes may allow an assessment of state of health, disease probabilities and of probable life span all items of interest to insurance companies. Is a person the owner of his or her genes, or of his or her genetic test results? Are there legal rules for the medical use of such results?

Thirdly, if the person's genetic make-up has to be established, who will bear the costs of the genetic tests? One can only hope that the costs will lessen as time moves on.

If these three problems are solved, the road towards personalised medicine is open. A first step could be assigning the patient to a genetically similar population group. Between person differences tend to be smaller within a genetically defined population than in a random population. Before one knows a given patient's genes, his or her duty to such a population would somewhat reduce the chance of encountering unexpected reactions. Thus, treating the patient as a member of a known population, even of a geographically or ethnically defined group, would be a smaller step in our efforts to create personalised medicine. Even if one has located a gene which is changed in a given person, however, two problems remain. First, a given gene may be mutated in many different ways.(24) There may be an absence of a protein, a functional decrease or a change in properties, for example, affecting various drugs differently. This may cause difficulties. For example, cytochrome

CYP2D6 metabolises debrisoquine in both a European and an African population, but an African variant metabolises debrisoquine but not metropolol. Secondly, the expression, and thereby function, of a gene may be changed by gene interactions, hormones or environmental factors like foods and drugs.(25) Thus, identification of a functional gene still leaves uncertainties. Whatever we do, now or in the future, creation of personalised medicine is a worthwhile aim, because it represents an effort to improve a person's chance of a healthy life; however, personalised medicine will never be a truly reliable science. For example, environments may change and, more specifically, gene expression may change; all predictions based on gene structure therefore represent functional likelihoods but not certainties.

We all will have to live a life with hopes and probabilities.

CONCLUSION

Individual variability in drug efficacy and drug safety is a major challenge in current clinical practice, drug development, and drug regulation. For more than 5 decades, studies of pharmacogenetics have provided ample examples of causal relations between genotypes and drug response to account for phenotypic variations of clinical importance in drug therapy. The convergence of pharmacogenetics and human genomics in recent years has dramatically accelerated the discovery of new genetic variations that potentially underlie variability in drug response, giving birth to pharmacogenomics. In addition to the rapid accumulation of knowledge on genome-disease and genome-drug interactions, there arises the hope of individualized medicine. Computational biology, or bioinformatics, has been instrumental in the development of pharmacogenomics. The gene expression arrays and high throughput genotyping techniques generate a large amount of data in a single experiment, much more than can be evaluated using commonly available spreadsheets or manual approaches. Therefore, software has been developed that not only captures the experimental data, but includes comparison of results with existing genome databases, for sequence homology, and pattern recognition to pull together genes with similar patterns of expression, as part of the initial algorithm. Since the completion of the human genome, there has been steady, albeit slow, progress in the identification and implementation of biomarkers into clinical practice. This progress is likely to continue, and hopefully accelerate as our ability to interrogate the human genome becomes more cost- and time-efficient, and we start embracing, and intelligently interpreting, different sources of data to define the clinical validity and utility of biomarkers. Outcomes research will thus become particularly important, and will depend on having access to curated electronic healthcare databases where patients can be followed longitudinally from the time of having a

biomarker assessed to the time a drug is prescribed, and forward into the future to define the clinical outcome of the patient (in comparison to relevant a priori defined controls).

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