NEW HORIZONS

Future Challenges of Pharmacogenomics in Clinical Practice

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Introduction

Right drug in right dose for right person is what pharmacology is trying since times immemorial. The fact that genes play a role in responsiveness to drug therapy is now known for nearly half a century and giving birth to the term pharmacogenomics. It is a well known fact that systematic discovery of genetic variation will allow better diagnostic and therapeutic modalities (1). Application of appropriate methods for discovery of genetic variance and their future in pharmaceutical industry for providing managed care as economic incentive will be a break through.

However, a lot of hurdles are yet to be overcome. The ethical, social and legal issues need to be addressed. Pharmacoeconomic analysis for new drug development using pharmacogenomics as a tool and the diagnostic procedures all need to be critically analysed.

Pharmacogenomics is essentially involved with improvement in patient care. It is concerned with genetic effects on drugs themselves and with the genetic variance that contribute to the variable effects of drugs in different individuals. The application of genome based techniques has broadened the opportunity for identifying genetic effects on drug action. Variance in genes accounting for variance in drug action are already being studied. Diagnostic tests are being developed to evaluate efficacy and safety of drugs in various individuals so as to help the physician decide the best drug and dose for his patient while minimising adverse drug reactions.

Information about genetic effects on drug action and variability of biological response plays a significant role in design, discovery and successful development of a new drug. Identifying significant genetic variation in the pre-clinical development phase will help to avoid new chemical entity (NCE) to enter clinical development and avoid costs (1).

Ethical Issues

The most important ethical issue that concerns pharmacogenomics is privacy of the study subjects (2). Participants should be adequately informed about how their genetic material will be handled, what all tests may be done, how the data will be utilised, where the genetic material be stored and how secure the DNA banks are. They should have knowledge about the persons who will have access to their genetic material. They should also be told that their DNA may be required for future use and how that data will be maintained. Informed consent for future use should also be taken before hand.

Privacy issues of family: A genomic study may need some information about subject's family, which may not be acceptable. Some critics are of the opinion that even the patient subjects should not be disclosed with their own genetic material to avoid the fear of future harm that may be predicted.

Better pharmacological care means better life expectancy. It may not be affordable for a common man. It is possible that only those who have money to afford the high expenses may benefit. Ethics demand equality, the cost of these pharmacogenomic techniques should be thus subsidised by the government. In countries like India where potable food is more important a public issue, is it worth allocating funds to learn how genes indicate a predisposition to disease and developing cures for the

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same? On the other hand in countries like USA, where adverse drug reactions account for major morbidity and hospitalisation (the fact that medicines are "a one-size-fits-all", leading to adverse drug reactions can be avoided), a lot of which can be avoided if genetic profile is known and drugs given accordingly. Initial high cost of technology development for genome analysis alongwith threat of losing one's autonomy needs to be reviewed.

The interest of pharmaceutical companies in financial gains that they may have if treatment is highly specific with minimal adverse effects, could threat the valid research or threaten protection of the rights and well being of individuals may become need of the hour.

Genes are not the only thing, environment has its own role in pharmacokinetics and pharmacodynamics of drug response. Thus implicating everything on genetics and promoting drugs may not be ethically acceptable.

Legal Issues

With pharmacogenomics in future, some legal issues need to be discussed before full implementations occur.

The person should know who owns the genetic data once he has given consent to analyse that. What is the legal liability if that data is stolen or lost or made public? Who is responsible for the damages? What is the compensation? Besides this, if he has not given consent for future use of his genomic data, and that is breached, what is the legality in such a situation? Can a person refuse for using his data without payment at any stage of drug development and use? How much is the doctor or hospital obliged to inform the person? One viewpoint is that the study subject should be informed only about the particular condition being tested and the rest should not be disclosed. i.e. person should not be told the future.

What is the legal issue if discrimination is made by job providers or insurance firms. In case the job providers know the person's gene data and avoids job (good for company as only best fitted individuals will be there to improve success but a loss for person who may have to face unemployement and switch over to malpractices) or insurance cover is avoided (3). These issues need to be answered.

Pharmacogenomics in Clinical Trials (Industry Perspective)

A drug development process can be highly expensive if the drug has to be withdrawn due to therapeutic failure or serious adverse events. The same can be cost effective if genetic profile of participants are known (4). Based on this, maximum success with minimal adverse events can be achieved. As of now, pharmacogenomics based techniques are still in their infancy. The reason is perhaps what is said is not true.

The economic analysis of pharmacogenomics is yet to been done. In order to search a specific population with a particular genotype in which a given new drug may be effective may be both frustrating and time consuming. Initial screening of individuals may be costly affair. Added to that the need to have a diagnostic technique to find out the specific SNP (single nucleotide polymorphisms) cost effectively may be problematic. Moreover, the number of patients, on the whole acually fitting into this criteria and who may be possible users of the drugs and who can share all the economic burden may not be rewarding. With the completion of human genomic project and with a possibility that sometime in the future, each and every individual will have his own gene chip, the whole scenario may not be that bleak.

Another situation may be that of the development of "orphan genotype". If the new drug that is being developed is of value in some selected group of individuals (for example a particular race) then the issues relating to distributive justice and fairness to accept the new drug with little commercial benefits needs serious thinking (5). Suppose, an asthmatic comes to a physician and asks "Sir, I heard there is a new drug for asthma !" and doctor says "Yes, but it is only for whites".

Generalisation of trial data on population outside the tested genotype will not be socially and ethically feasible. These results will have to be tested in general population and for efficacy and adverse events.

Post-Marketing Pharmacogenomic Studies

Following drug approval, pharmacogenomic data can be used to understand the potential adverse events of a

drug or over-responsiveness to the given therapy thus resulting in better patient management (6).

Pharmacogenomic testing may yield collateral information, which may be medically beneficial. Nevertheless, it may be even disturbing to the physician if no cure for that is there, e.g., polymorphism in dopamine receptors may be a pharmacogenomic parameter that may help in smoking cessation therapy individualisation (7). They may also be collaterally a marker for personality or behaviour, like drug abuse, alcoholism and attention deficit disorder.

Pharmacogenomic testing can be focussed or expanded. A focussed pharmacogenomic test assays the minimum number of specific markers relevant for a particular drug decision. The expanded tests involve assaying of wide range of markers to provide genetic information even if the immediate requirement for the same is not there. This may be more cost effective, provide information on future drug therapy, more helpful in scientific research, benefit by testing hypothesis about genetic marker-drug response correlation. However it suffers from the drawback of extra cautiousness to maintain privacy and discovery of unwanted information which may lead to psychological impacts.

Pharmacogenomic Testing in Children

Pharmacogenomic testing in children and adolescents may be done for conditions where immediate therapeutic outcome may be feasible as per current levels of advances in pharmacology. However, complete genome matching, finding conditions which may arise in old age and for which no current standards of treatment are available may not be very ethical. This may enhance confusion with little benefit. The final decision, whether to undergo, pharmacogenomic testing or not will be with the patient only. The physician may however help him in rational decision making as e.g. a patient with Thiopurine S Methyl Transferase (TPMT) deficiency is likely to undergo myelosuppression with anticancer chemotherapy. Such a patient may be advised to undergo pharmacogenomic testing so to predict outcome and alternatives. Similarly, females with factor V leiden heterozygous state and using oral contraceptive pills may be helped to decide about the increased risk of deep vein thrombosis versus benefit of avoiding pregnancy.

Pharmacogenomics and Diagnostics (8)

Though, the ultimate aim of pharmacogenomics is discovery of highly effective novel therapies to reduce the cost of drug development, this cannot be achieved unless highly accurate diagnostic tests support pharmacogenomic results. These diagnostics are based on isolation of effective/non effective isogenes (which are gene sequence variants and have been found to be importantly involved in breast cancer gene, BRCA1, p53 oncogene, cystic fibrosis gene and so on).

The first diagnostics was for BRCA1 breast cancer predisposition detection by Myriad Genetics in 1997. Following this, many biotechnology and pharmaceutical companies are engaged in finding accurate diagnostics for pharmacogenomic studies. One approach is by collecting and analysing pharmacogenomic data of populations that have bred pure with minimum interchange with the rest of the world. Another is to collect genetic database from various disease populations like cardiovascular diseases, cancers, neurological diseases and subject them to various high throughput requiring technologies. FISH (Fluorescent in-situ hybridisation) is being used for prenatal diagnosis of chromosomal abnormalities. MASDA (Multiplex Allele-Specific Diagnostic Assay), developed by Genzyme Genetics, interrogates multiple DNA samples with ASO (Allele-Specific Oligonucleotide) probes and any prolic that hybridise with the sample DNAs are required. This reveals the quantitative and qualitative nature of any mutations present. In a single run, this technique can analyse more than 500 samples for more than 100 known mutations, which may be point mutation and insertion / deletion mutation e.g. a single assay detecting cystic fibrosis, beta-thalessemia, BRCA1, Gaucher's disease, Fanconi anemia, Tay sachs disease and sickle cell anaemia.

Airtech diagnostics, has developed enzymatic mutation detection method for the detection of polymorphisms in DNA with nearly 100% sensitivity. Mitokor has developed a technique to analyse mitochondrial DNA, rather than whole genome, as a diagnostic marker of metabolic

disorders. This company has achieved considerable success in Alzheimer's disease. Horus Global Health Net uses computer algorithms to analyse complex data from multiple biochemical markers and clinical tests and have attained high accuracy to diagnose prostate cancer using their product prost asure. May others are in pipeline.

The fact that only genes are responsible for the observed effects to drugs is also not a true statement. Even with the best of diagnostic accuracy of specific gene effects on therapeutics, variance is observed.

Social Issues

The economic burden of a new therapeutic science will be borne by the society. Knowing the genotype of the person will open the genotype of whole community of that person. Family tree can be constructed. A lot can be deduced from this family tree. This leads to breach in privacy of whole community whose consent is not taken (9).

This may also lead to formation of a group susceptible to a particular drug, having a possibility of a particular disease in future or having a predisposition to something not curable as per current standards. In one way it is good: the lifestyle modifications can be initiated early, the effective therapy can be started for prevention and treatment at the earliest and longevity can be expected. But other side is, if the person knows that sometime in future he will develop some cancer for which no treatment exists, he will die hundred deaths before that.

Pharmacogenomic variations may lead to opening up of some constitutional issues like those of getting some special incentives or minority status.

Proposed Benefits of Pharmacogenomic Application in Medicine

- Identification of many disease related genes and drug specific for genotypes: more drugs specific cure.
- Categorising human diseases to specific subcategories will become possible. The better is the disease diagnosis, better the treatment.
- Development of new medical tests for specific diseases will help in the analysis of predisposition to diseases as well as primary and secondary preventive measures for benefit of the recipient. Thus pharmacogenomics will provide tailored approach for patient care with maximal benefit and minimum adverse effects.

Technical Difficulties

Most important problem is practical need of methods required in drug development without increasing cost, time or complexity of the development process. Human Genome Project is perhaps the answer for all this.

Table 1. Comparative analysis

	Pharmacogenomics		Traditional medicine
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Conclusion

Pharmacogenomics is emerging as a boon for medical fraternity. However, before the full application of this branch, the higher authorities should frame and address the various social, legal, ethical issues alongwith incentives to overcome technical difficulties.

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