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Pharmacogenetics and Pharmacogenomics: Perspective to Sustainable Development and Bioethics

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Abstract—*Until about 50 years back the idea of personalized medicine was not much into place. But results of pharmacogenetic studies have provided examples of relationship between genotypes and drug responses which affect the phenotypic variations in drug therapy. It arises hope of individualized medicine. Pharmacogenomics is an apparently new science to predict the right treatment in individual patients and to design new drugs by studying their genetic profile. Such an approach, if completely feasible and affordable can revolutionize the way in which healthcare is monitored today; much akin to change from land based phone lines to cellular mobile phone technology. Out of eight Millenium Development goals set by United Nations atleast three are clearly inclined to healthcare and to achieve such goals globally, mere will and capital is not enough until high end technology entwines them. But , the point comes where awareness, traditions, social cultures, taboos and cost effectiveness comes into play and cutting edge scientific technologies may not be feasible to be globalized from advanced nations to least developed nations on same platform. This paper discusses the growth and development of the science of pharmacogenetics and pharmacogenomics and their possible role in respect to realizing sustainable development as well as bioethical grounds attached to them.*

1. INTRODUCTION

Physicians since time immemorial have observed that in different individuals there are some differences in response to the same drugs in same dosage for the same symptoms. Though in ancient times the exact causes were not known but still references have been found in history which can be considered as the earliest developments in the field of pharmacogenetics. In 510 B.C. Pythagoras noted that ingestion of fava beans resulted in a potentially fatal reaction in some, but not all, individuals.Then with the experiments of Mendel and propounding of some principles of heredity, the science of genetics and heredity developed alongside the science of pharmacology as well. The term "pharmacogenetics" came to be used in scientific domain around late 1950's when Arno Motulsky first conceptualized and investigated the effect of inheritance on individual drug response and was used in reference to genetic aspects of pharmacokinetic factors of drugs. But, it was only in 1990's that the term "pharmacogenomics" came to be used in scientific literature. Though used interchangeably in some place there is a difference between the two terms. While pharmacogenetics is the branch of science which deals with the study of influence of genetic variation of an individual on drug response, pharmacogenomics is the application of the genomic technologies to the study of pharmacogenetics and is an offshoot of pharmacogenetics only. Pharmacogenomics examines the effects of various drugs on the expression of multiple genes, largely in vitro (DNA, RNA and proteins) and is involved in research and development of new compounds as well to aim these molecules. The understanding of the exact variations in genes - causing differences in drug responses among different individuals can be exploited to the benefit of humanity and medical science by way of personalized medicine or personalized drug therapy. This is where the pharmacogenomics comes into play. Personalized medicine though a possibility is supposed to have its own pros and cons over wider aspects.

2. GENETIC VARIATIONS: DETERMINANT TO DRUG THERAPY AND RESPONSE

2.1. Studies on developing avenues to Pharmacogenetics and pharmacogenomics

One of the most ambitious projects in the biomedical science has been the Human Genome Project which aimed at identifying the sequence of chemical base pairs which make the human DNA, identifying and mapping of genes of human genome. It was declared to have been completed in 2003 and provided scientists with valuable information to have a better understanding of biological mechanisms of physiology to pathology at the genetic level. However, till date the genetic level therapies are few and too costly (cost effective) to be affordable for the masses.

A patient response to a drug is linked to genetic variation of his genes. Genetic variation of one particular type has garnered more interest than others and it being Single Nucleotide Polymorphisms (SNPs) and the potential for using these to determine the individual drug response profile. SNPs are responsible for substitutions of one nucleotide for another at a given location at the lowest cellular levels. SNPs make feasible to access the genetic variation in an individual and further help to ascertain the associated drug response. Based on clinical findings and genetic profile like SNPs, individual's can be divided into subpopulations that have a particular response to a particular drug. To study the SNPs, a Wellcome Trust and pharmaceutical industry consortium was established in 1999 termed as TSC (The SNP Consortium) and it has disseminated all the data into public domain of more than 1.5 million SNPs which have been identified and mapped. Such data and the inputs from data of Human Genone Project effectively help to build up individual SNP profiles which correlate with individual drug response. Genomic profiling lead us to many advantages over the conventional therapy system ("one size fits all"). It prevents the negative side effects i.e. ADRs (Adverse Drug Reactions), reduce the cost of healthcare over any unwanted diagnostic tests and also improve the effectiveness of the drug and treatment therapy. Also tailor drug prescription and dosage for individual as well streamline the pharmaceutical industries to produce effective and relevant drugs by saving big capital and prevent unnecessary flooding of market with different varieties of placebo.

One important discovery in research has been focused during the last few decades is the discovery of pharmacogenetics of drug metabolising enzymes and particular the Cytochrome P450 (CYP) drug metabolizing enzymes. These enzymes are primarily found in human liver and play a vital role in breakdown and body clearance of chemical drugs. Most of the prescription drugs are metabolized by 5 main cytochrome P450 enzymes, CYP2D6, CYP2C19, CYP2C9 and CYP3A4/5. Based on studies about CYP our understanding has been enhanced about the clinically relevant genetic variations that may help predict drug response. Two important concepts to understand the response to drug is determined by genetic factors. At the same time, drug response is also determined by several interacting genes and influences from the environment as well.

2.2. Implications of genetic variations to various facets of therapy and response

Genetic variation is considered an important source of variability in drug response and contributes to 25% - 50% of inappropriate drug responses. The type of therapy, drugs and their respective dosage varies significantly from one person to other. In addition to genetic factors many other factors such as environmental as well as physiological are also significant in causing variation in drug responses. Some genetic factors are: mutations in genes of enzymes which are involved with drug metabolism, drug transporters and so whereas environmental factors vary from individual habits such as alcohol and tobacco consumption to exposure to chemicals, dietary habits as well, as co-administered drugs. Physiological factors are many and most relevant being disease status, age and sex. Genetic factors are hereditary and are permanent while the physiological and environmental factors are liable to change over period of time.

The effectiveness of pharmacologic drug therapy to patients depends significantly on the extent of metabolic efficiency of individual patients and as a result pharmacokinetic variations are evident in them. The interaction between drugs act by enhancing or inhibiting the metabolic enzymes involved for drug metabolism and it has an effect on the bioavailability of the primary drug. The concept of phenotyping and genotyping individual patients is proposed as a major step towards realizing the practicability of genomic medicine. Phenotyping is carried out by using probe drug to measure the enzyme activity and where the metabolism of probe drug is known to be dependent on particular CYP enzyme. But, limitations of measuring individual phenotypes at various time points requires collecting multiple specimens at fixed time intervals post administration of drug. The method is also liable to be affected by various factors such as other interfering drugs, health status and environmental factors.

Phenotype can be measured by using assays to determine genotype from a patient sample. Genotyping results are not prone to external factors such as drugs, diet or environmental. Genotyping assays by molecular methods are fast, reliable and accurate. Experts are required for interpretation of genotypic result to the phenotype. Identification of patient genotypes for clinically relevant CYP genes help physicians tailor drug treatment to patients through the selection of appropriate therapies. These measures may improve a physician's ability to impact patient outcome by ensuring maximum drug efficacy with minimal adverse drug reactions.

3. GLOBALIZATION AND HEALTH

3.1. Millenium Development Goals, Sustainable Development Goals and the challenges to healthcare

With the world population reaching the mark of 7 billion in December 2014 as per UN estimates and to add another one billion in coming ten years i.e. by 2024 the resources of the earth are going to be severely challenged. There is a competition for everything even today and the idea of a utopian state is far from being realizable in spite of high technological developments, considering the net increase in population among whom the profits of development have to be shared.

World bank came up with a very prospective estimates of having attained the first Millenium Development Goal target to cut the 1990 poverty rate in half by 2015 by attaining the same five years ahead of schedule , in 2010 itself. Despite such numerical estimates affirming our alignment with the Millenium Development Goals the problem of poverty is hardly solved in full. In 2011, 17 percent of people in the developing world lived at or below $1.25 a day which is the limit set internationally for below poverty line estimation. Even at the present rate of progress if maintained, some 1 billion people will continue to live in extreme poverty in 2015. The United Nations Conference on Sustainable Development (UNCSD), also known as Rio+20 or Earth Summit 2012 was the third international conference on sustainable development aimed at reconciling the economic and environmental goals of the global community. One of the main outcomes of the Rio+20 Conference was the agreement by member States to launch a process to develop a set of Sustainable Development Goals (SDGs), which will build upon the Millennium Development Goals and converge with the post 2015 development agenda and the main issue is to eliminate poverty so as to make world poverty free. Particularly in the developing countries there is a wide gap between the rich and the poor and financial capability is the decisive factor for affordability to access to resources for good healthcare, education, safe drinking water, electricity and a clean environment to stay. The concept of personalized medicine in terms of pharmacogenomics and pharmacogenetics stems its root in the fact that it has the capability to address the main problem of health in the most effective and advanced manner.

In 2013 statement, World Health Organization quoted that “Personalized Medicine is a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention”. In simple terms, it has the potential to address the healthcare at an individual’s level according to his or her body needs and if the costs can be cut down for accessing the same, health will be a manageable issue at world level as such. The benefits of personalized medicine maybe but not limited to areas such as: to reduce the cost on multiple diagnostic tests, reduce Adverse Drug Reactions, help in profiling of health care most tentatively gene profiling for all individuals, help governments in policy making regarding healthcare, help underdeveloped nations specifically with their health care requirements, reducing cost on pharmaceutical experimentation to the tunes of billions of dollars annually.

3.2. Socio-Cultural, Politico-Economic and Bioethical issues to personalized genomic medicine

The acceptance of any new technology is confronted by various social, religious and cultural norms. And in today's world when politics plays an ever important role in everyone's life, politicization of anything at all may lead to wrong turn of events.

3.2.1. Social and Cultural Issues

3.2.1.1. Higher Public Voice: More accessibility to individualize healthcare and equipped with better social media presence the public can have a more firm voice trying to manifest the market demand and change the way the pharmaceuticals companies intend to market the personalized medical facilities. Also, it will create a pressure on governments to frame policies in accordance with public view and provide quality and ease of access to personalized medicine.

3.2.1.2. Unintended Revelation of Genetic Information: Though genetic information is strictly personal affair, but having it for use in regular medical needs lead to unintentional revelation and persons with malafide intentions may try to use such information in some way or other to the detriment of the individual.

3.2.1.3. Classes based on genetic profiling: Persons with similar geographical location or ethnicity may have similar genetic makeup. Having genetic profile of all the individuals at disposal may lead to division of people on the basis of similar or better genetic makeup from those of inferior genetic makeup calling for discrimination.

3.2.1.4. Training of Medical Personnel: With the advances in the field of pharmaceutical sciences, the professionals in the field also have the onus on them to keep them updated with all the developments and technological know-how in the field. But, the same is not as easy as it may sound since there are hardly few experts in the field and the whole array of professionals and associated workers need to be trained for the same and the infrastructure is lacking and it may take time to put in place the infrastructure itself.

3.2.2. Economic and Political Issues

3.2.2.1. Luxury medicine: Pharmacogenomic technologies may lead to the development of drugs which may appear to be a luxurious commodity for populations in need of numerous interventions ranging from access of clean water to medical attention for infectious diseases.

3.2.2.2. Cost effectiveness: The concept of tailor made drugs for individual genotypes is in contrast to the conventional model of mass-producing drugs suitable and safe for the widest possible range of people at competitive prices. Designing drugs for individuals is always more expensive and such technological knowhow will be with only industrialized societies and appeal to the affluent class only. Moreover, whether the pharmaceutical companies will be interested in

donning up the new way of commerce as of keeping their cost-benefit ratio is a matter of concern.

3.2.2.3. Sharing of genetic information of developing and least developed countries with developed countries: Countries which do not have much technological advancement and would like to secure the benefits of pharmacogenomic medicine will be obliged to depend on technologically advanced nations for the same. In due process for it, they will have to share the genotypic profiles of the citizens with an external nation and it can be crucial in times of war and disturbed diplomatic relations.

3.2.2.4. The Lack of Regulatory Responses: In the absence of regulatory responses and laws in this field, a unanimous political consent is nearly impossible and the area will be full of legal nuances public and political deliberations.

3.2.3. Bioethical Issues

3.2.3.1. Bioterrorism against smaller genogroups: Having the genotypes of smaller subgroups of population with similar genotypes can make it possible on one side to design drugs against specific genetic disorders or other disease but at the same time can also help to target such a population by effectively designing drugs specifically against them.

3.2.3.2. 'Pharming' ethics: Using genetically altered animals to produce human drugs (‘pharming’) raises special ethical issues beyond those usually associated with humane care of animals. Pharming increases the demand of animals to be used for the welfare of mankind. In spite of the following of mandatory guidelines of animal ethics, large scale use as well as specific demands may expose to conditions which are not humane and suffer pain and misery.

3.2.3.3. Intellectual Property Rights: The intellectual property rights related to any industry are the biggest asset over which the stability and competition is balanced in industries. The field of pharmacogenomics and personalized medicine will in turn create many such instances where the ethical issue of patenting genes and genomic information arise over which the laws are widely different in different countries and social taboos which attached to such issues as well.

4. CONCLUSION

From this analysis, it is clear that pharmacogenetics and pharmacogenomics will impact upon the research, regulatory and healthcare organizations, governments and policy think tanks alike. One thing is surely evident and that much deliberations need to be done analyzing the social, ethical and regulatory mechanisms for such a system of personalized medicine. It must be evolved in such a way so as to address the need of healthcare of the millions of people all over the world who can't afford basic healthcare facilities as such. Developments in this field must be synced with the goals of United Nations for equitable access to all instead of creating a new generation rift of those having been able to afford the personalized genomic healthcare and the other who can't. Ironically, pharmacogenomics – which represents the segmentation of patient populations into smaller and smaller groups – will require various actors to work more closely together than ever in an attempt to better understand and coordinate drug development, regulatory issues and health policy.

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