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BIO INFORMATICS

PHARMACOGENOMICS- A BOON FOR CHRONIC DISEASES

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ABSTRACT

As the health care industry is showing diversification and is attempting to offer solution to the masses. There has been a rapid advancement in the field of research and development such as enabling techniques like gene therapy, microarray testing, MALDI TOF, pharmacoinformatics and pharmacogenomics. The current health care scenario is taking into account the genetic make-up for each individual and is distinctly more towards “trial-and-error” methodology, which subjects the case and their physician to higher probability of uncertainty of outcome. The unturned milestones of several drugs like Rezulin, Baycol and Fen-phen have provided with a lesson and ways to test prospective drugs, for toxicity. Lately, customized therapy is playing the key role in health care and diagnostic industry.

Pharmacogenomics gives the new definition to the ways drugs are developed, selection of the drugs to the patient; based on their genetic make-up. Pharmacogenomics use genomic and sequence data host and pathogens to identify potential drug target. This field heavily depends on bioinformatics. By the definition, despite its- genomic suffix, pharmacogenomics is not limited to analysis of Deoxyribonucleic Acid (DNA), but rather also includes Ribonucleic Acid (RNA) and protein This paper deals with the efficacy of the technique, its relevance to the Indian market and its cost parameter in the developing country.

The paper deals with basic concept of pharmacogenomics, role in drug development, its .limitations, ethical issues related to it and its need in the Indian as well as global market with special reference to chronic diseases such as Alzheimer’s disease, colorectal cancer which is common to both the sexes globally and AIDS, the disease most discussed from approximately three decades.

KEYWORDS

Pharmacogenomics, Drug Discovery, Alzheimer's disease, Colorectal Cancer, AIDS

INTRODUCTION

The term pharmacogenomics comes from the combination of the two words; pharmacology and genomics. Pharmacogenomics is the study of single gene mutation and their effect on drug response. The current status of this field is confined to the areas of medical research and epidemiological studies.

Many treatments like oral anticoagulants and cancer chemotherapy have been invented where tailor-made drugs are used to suit the genetic status of an individual. This is done, so as to improve efficacy, to avoid toxicity and treatment failures.

This involves use of markers in individuals' genetic code to pin point the cause of disease. The ultimate aim of pharmacogenomic research is to provide information for personalized medicine i.e.; providing accurate medicine with the apt dosage to the patient. The technique leads to a better understanding of drug-drug response and drug-organism response. For example; if one group people break down a medicine very quickly or very slowly compare to others, then their genes may offer a clue as to why they respond that way. If so then it may be predicted, based on his or her genes, how someone would react to a medicine (biomarkers) that means the tools of pharmacogenomics run the gamut from immuno-histochemistry to sequencing, microarrays to polymerase chain reaction (PCR).

Role of pharamcogenomics in Drug Discovery and Development

Pharmacogenomic studies can be used at various stages of drug development. In clinical studies, this can be used for stratification of patients based on genotype, which corresponds to the metabolizing capacity. This prevents the occurrence of severe drug reactions and helps in better outcome of clinical trials. This can also reduce attrition of drug compounds. Further, the variation in drug response can be better studied with the wider application of pharmacogenomics methods like genome wide scans, haplotype analysis and candidate gene approaches. The cost of pharmacogenomic testing has become very low, with the advent of newer high throughput genotyping systems. However, the cost of pharmacogenomics method continues to be very high. And this is being witnessed as the treatment with several drugs is being more and more pharmacogenomically guided for example: Warfarin, Sulfonylurea drugs and Irinotecan.

Pharmacogenomics and Warfarin therapy

Warfarin is an oral anticoagulant indicated to the patient with a history of atrial fibrillation, myocardial infarction, deep vein thrombosis, or pulmonary embolism, and for patients with certain types of artificial heart valves. Warfarin acts by interfering with the synthesis of vitamin K- dependent clotting factor in the liver. Bleeding is the most common adverse effect associated with it. While the risk for bleeding events is the highest in the first 90 days of therapy, it persists throughout the course of treatment. But pharmacogenomics-based warfarin dosing has the potential to reduce the risk of bleeding, increase dosing accuracy, shorten the time to dose stabilization, and health identify individual who may require more frequent monitoring with long term therapy.

Pharmacogenomics and Sulfonylurea in Type-II diabetes

The sulfonylurea's stimulates insulin release from pancreatic beta cells and have been the corner stone of Type-2 diabetes pharmacotherapy for over 50 years. Although sulfonylurea drugs are effective anti-hyperglycemic agents, inter-individual

variability exist in drug response, disposition and adverse effects. The field of pharmacogenomics has been applied to sulfonylurea clinical studies in order to elucidate the genetic underpinnings of this response variability.

Table No.1

Advantages, Disadvantages and ethical issues relate to the field of Pharmacogenomics

Advantages	Disadvantages	Ethical Issues
1. More powerful drugs 2. Better and safer drugs 3. More accurate methods for determining appropriate drug usage 4. Advance screening for disease 5. Better vaccines 6. Improvement in the drug discovery and approval process 7. Decrease in overall cost of healthcare	1. Complication in target in a particular drug 2. Small variations in genes which may evolve due to unwanted mutations, influence drug metabolism and can be very time consuming 3. Drug-drug interactions and environmental factors need to be determined before reaching to any conclusion regarding efficacy and genetic influence 4. Problem in practical need of methods, complexity in drug development 5. Currently, not available to common man	1. Issue related to privacy of the study subject 2. Transparency while dealing with the subject(patient), i.e. information should be delivered of each and every step correctly to the subject 3. The related concern is privacy of the subject's family as a genomic study may need some information about subject's family, which may not be acceptable

Current Scenerio

In today's world, on an average of 30-60% of drugs work effectively to rid of patient's illness. But, with the application of pharmacogenomics, the success rate of drugs can reach up to 100%, curing all patients. The successful pharmacogenomics drugs available are:

Herceptin: An effective drug for breast cancer (Genentech, San Fransico).

Gleevec: A drug used for cancer such as chronic myelogenous leukemia and gastrointestinal stomach tumor (Novartis, Basel, Switzerland).

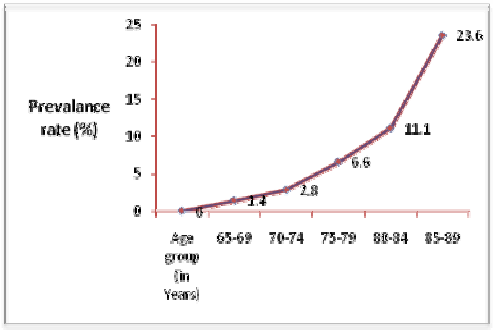
Abacavir: Used in treatment of HIV/AIDS (GlaxoSmithKline,Brentford, UK)

Role of pharmacogenomics in Curing Chronic Diseases

Below, three very grave and prevalent chronic diseases are discussed which are generally misdiagnosed and mistreated due to lack of accurate symptoms and medications. But if pharmacogenomics technique is applied to them they can be accurately diagnosed at their infancy stage along with proper medications, this will help in longer survival of the subject.

Alzheimer's Disease

Alzheimer's diseases can occur at any age, even as young as 40 years, but its occurrence is much more common as the years go by. In fact, the rate of occurrence of the disease increases exponentially with age.



Graph No.1
Effect of age on risk of Alzheimer's disease

Alzheimer's disease in pathogenesis and drug metabolism is genetically regulated, in which numerous genes participation is there. **Alzheimer's patients** are moderate responders to conventional drugs such as donepezil, rivastigmine, galantamine, memantime with doubtful cost effectiveness. Pioneering pharmacogenomics studies demonstrated that the therapeutic response in this disease is genotype-specific, with apolipoprotein E.

Pharmacogenomics factors may account for 60-90% of drug variability in drug disposition and pharmacodynamics. The incorporation of this technique protocols to Alzheimer's disease research and clinical practice can foster therapeutics optimization by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety. The cost of caring for patients with Alzheimer's is huge. If we compare U.S and India, we find whopping healthcare economic expenditure in US. In India, 90% of the cases of dementia are actually Alzheimer's disease but are misdiagnosed. It is estimated that in 2010, India is home to 3.7 million people with Dementia and is likely to increase exponentially in coming future.

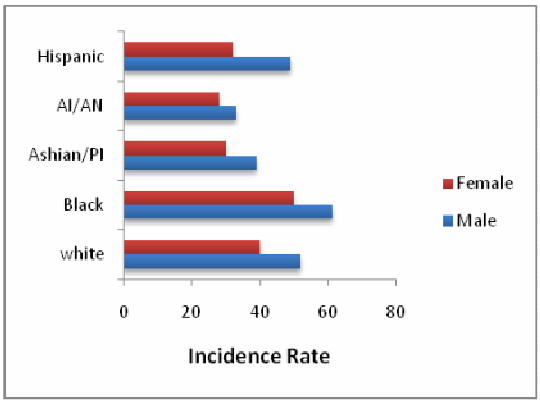
The value of the Alzheimer's disease market is an estimated $8 billion in 2009, but is expected to increase to $ 9.6 billion in 2014, for a 5-year compound annual growth rate(CAGR) of 3.7 %. After advent of pharmacogenomics the cost factors has reduced to 10-20% of direct cost. This technique also helps in gene targeted medication with optimum results.

Table No.2
***Comparison in expenditure on Alzheimer's' disease* in United State of America and India**

Area of expenditure	U.S.A	INDIA
Annual direct or indirect cost of caring someone with this disorder	$100 billion	The annual cost of dementia is estimated to be INR160,000 billion and is expected to double by 2030.The cost of taking care of such persons is INR43,000 annually
Average lifetime cost	$174,000	
Annual cost for someone with mild symptoms	$18,400	
Annual cost for someone with moderate symptoms	$30,100	
Annual cost for someone with severe symptoms	$36,132	
Contribution to heath care business	$24.6 billion	

Colorectal Cancer

Colorectal cancer is one of the most common cancer types in both men and women. There are multiple treatment strategies; however, there is currently no clear strategy for therapy selection. Pharmacogenomics includes studies of variations in germline DNA, somatic mutations in the tumour genome, gene amplification and variations in RNA expression, including epigenetic mechanism. Pharmagenomics promises to be useful tool for identifying markers that can be screened in colorectal patients prior to chemotherapy selection to predict efficacy and /or toxicity.



Graph no.3

Colorectal Cancer Incidence Rates By Race/Ethnicity And Gender

The availability of multiple treatment options for colorectal cancer makes it an ideal choice for pharmacogenomics research. Current colorectal cancer treatments include pair-wise combinations of **5-Flurouracil, Irinotecan and Oxaliplatin.**

Acquired Immunodeficiency Syndrome (AIDS)

It has almost been three decades since AIDS came into Indian picture and since then, there has been remarkable progress in the therapy of HIV disease. At the beginning, all that was offered was prophylaxis and treatment of the opportunistic infection that are the hallmark of immune deficiency disease. The first five drugs that were active against HIV, Zidovudine (AZT), was licensed in US in 1987. Since then, advances have made in drug development as well as the use of different drugs in appropriate combinations. The use of so called **HAART (highly active anti-retroviral therapy)** since 1995 it has led to appreciable decrease in AIDS related deaths.

HIV can now be classified as a chronic disease until a cure is found, patients are likely to require long life therapy. Despite of these undoubted advances, there are many issues that need to be resolved, problems related to long term efficacy, toxicity and resistance.

Pharmacogenomics is likely to be particularly useful for drugs that have variable kinetics and dynamics, and a narrow therapeutic index. Anti-HIV drugs certainly fits this category. The technique classically focuses on host nuclear genetic polymorphism that can be used to predict adverse drug reactions. Pharmacogenomics testing method have expanded to include molecular assays that characterize extra nuclear as well as the host nuclear genetic material. These assays use complex technical and interpretative methods to improve the therapeutic efficacy of antiretroviral therapy.

If we look at the current scenario, **NACO (National AIDS Control Organization)**, the central government agency responsible for tracking and controlling the HIV/AIDS epidemic, estimated that by second decade of this century, 3.8 million people have been infected by AIDS. It has been envisaged that the projected mortality rate in India through HIV will constitute 17%thewhole by 2033.

Table no.3
Global Summary Of AIDS Epidemic-2009

Number Of People Living With HIV	**Total:** 33.3 Million(31.4 Million-35.3 Million) **Adults:** 30.8 Million(29.2 Million-32.6 Million) **Women**:15.9 Million(14.8 Million-17.2 Million) **Children(Less Than 15 Years):** 2.5 Million(1.6 Million-3.4 Million)
People Newly Infected With HIV In 2009	**Total** : 2.6 Million(2.3 Million-2.8 Million) **Adults** : 2.2 Million(2.0 Million-2.4 Million) **Children(Less Than 15 Years):** 370000(230000-510000)
AIDS Deaths In 2009	**Total**: 1.8 Million(1.6 Million-2.1 Million) **Adults:** 1.6 Million(1.4 Million-1.8 Million) **Children(Less Than 15 Years):** 260000(150000-360000)

India's annual AIDS budget program from all sources is more than $57 million. Recently, the resistance assays demonstrate the utility of the pharmacogenomics testing for patients undergoing life long and complex antiretroviral therapy. This stream of science reveals promising new targets by providing a better understanding of cellular pathways, identifying new intervention areas such as phospholipids, glycolipids, innate immunity and antibiotics peptides. Additional antibiotic resources come from new genomes, including marine organisms, lytic phages and pro-biotic strategies. A system perspective regards all interactions between the hosts, pathogens and environment to develop new pharmacogenomics strategies against resistance development. Future applications of antiretroviral-directed pharmacogenomics test range from quantitative detection of mitochondrial depletion as an early surrogate marker for drug toxicity, to quantitative analysis of host immune haplotypes and metabolic genetic polymorphisms, for predicting disease progression. Clinical trials for such medicines have lately started some of drugs have reached upto phase-III, few are under juvenile stage and some are in pipeline.

Future perspective of pharmacognomics globally

Foremost goal of pharmacogenomics, to make the pharmaceutical companies develop drugs based on their proteins, RNA molecules and enzymes which are all associated with genes and diseases. The medicine will be accurate in the sense that it will have the least side-effects to the healthy cells.

Till date pharmacogenomics have accomplished many difficult tasks and it accompanies great achievements by using human genome sequencing. Through this we can certainly say that we can achieve **specific person, specific gene, specific disease, specific drug and specific treatment leading to the personalized medicine.**

If the other perspective of this technique is taken in account i.e.; cost effectiveness, then it is very one of the greatest boon for the world. For instance, Single Nucleotide Polymerase (**SNP)** screenings will benefit drug development and testing because pharmaceutical companies could exclude from clinical trials those people whose pharmacogenomics screening would show that the drug being tested would be harmful or ineffective for them. Excluding the people will increase the chance that the drug will show itself useful to a particular population group and will increase the probability that the same drug will make it into the market place. Pre-screening clinical trials subjects should also allow the clinical trials to be smaller, faster, and therefore less expensive, benefiting the

consumer. Finally, the ability to assess an individual's reaction to a drug before it is prescribed will increase a physician's confidence in prescribing the drug and the patient's confidence in taking the drug. Therefore, it certainly gives cost effective, safer and accurate drugs.

In India, many pharmaceutical companies have made significant investments in pharmacogenomics, with the expectation that it will help to eliminate the unpredictable nature of drug development, bring new products to market, aiming at preventing common diseases and also creating premium pricing for their products. It is estimated that by using pharmacogenomics – enhanced drugs and diagnostics' the companies could benefit upto INR 903 – INR 2,258 crore in extra revenue for each drug.

The notable players include Avesthagen, OncQuest laboratories, Acton bio-tech, TCG Life Sciences, Advinus therapeutics' and Jubilant biosys.

CONCLUSION

The common scenario of treating chronic diseases today is the trial-and-error methodology of drugs. However, with the drugs formulated after pharmacogenomics, physicians will be able to match the right drugs to the right patients based on their genetic profile. With that, the patients will be prescribed with the best drug therapy from the beginning, without the side effects.

In addition, because physicians will be able to prescribe the accurate drug therapy, the patient will have more chances of speedy recovery. The likelihood of adverse effects is eradicated. The scientist are optimist that there study can reduce more or less 100,000 deaths and 2 million hospitalization every year in United States alone.

BCC reports that the comprehensive analysis of current market for pharmacogenomics and its future direction. Currently, the field remains immature. This leaves enormous room for growth.

Developing countries such as India are consolidating search in genomic medicines. The focus in these countries is to leverage the genetic variation in the population to explore linkages between genes, diseases, environmental factors, develop new therapies and diagnostic tests and look at biotechnology-based innovations. One such initiative is the **Indian Genome Variation (IGV) Consortium**. This program aims to provide data on validated SNPs in over 1000 genes in 15000 individuals drawn from Indian populations, the IGV data based have already been developed. The important information from this project is expected to facilitate research on disease predisposition, adverse drug reactions and population migration.

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