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TAILOR MADE MEDICINAL APPROACH: PHARMACOGENOMICS

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ABSTRACT

By empowering the knowledge of gene sequence and their functions, biomedical research are more focused towards inter-individual variations that are expected to become eminent part of treatment planning in terms of efficacy and adverse effects of drugs. Existence of genetically distinct races is the reality and so is the pharmacological variations known to occur in varying frequency in different people. Adverse drug reaction conveys great risks of morbidity and mortality to a prescribed drug in a number of populations in the world today. This approach has lead to the development of personalised medicine or tailor made medicine and that is what pharmacogenomics deals with. In this review basics of pharmacogenomics, its futuristic applications in various diseases and various issues related to pharmacogenomics along with its limitations are illustrated.

KEY WORDS

Pharmacogenomics, Breast cancer, Alzheimer's disease, Ethical issues, Legal issues ,Social issues .

INTRODUCTION

The person-to-person variability of drug response is a major problem in clinical practice and drug development. It can lead to therapeutic failure or adverse effects of drugs (ADRs) in individuals of subpopulations of patients. The way a person responds to a drug either positive or negative reactions is a complex trait that is influenced by many different genes. Without knowing all of the genes involved in the drug response, scientists have found it difficult to develop genetic tests that could predict a person's response to a particular drug. Once scientists discovered that people's genes show small variations or changes in their nucleotide (DNA base) content, all of that changed- genetic testing for predicting drug response is now possible[1].

Pharmacogenomics is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all [1.] .Pharmacogenomics holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key for creating personalised drugs with greater efficacy and safety. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms (SNPs)[2].

Pharmacogenetics and pharmacogenomics

The terms pharmacogenetics and pharmacogenomics are often used interchangeably, which causes some confusion. However, the term pharmacogenomics is preferred when referring to clinical practice. This is because the field of pharmacogenetics deals with the genetic determinants of a single gene that affects drug therapy, whereas pharmacogenomics focuses on candidate genes, often more than one, and may include transcriptome and proteome information that affect drug metabolism, pharmacokinetics, and pharmacodynamics. Moreover, pharmacogenomics encompasses the genetic predisposition to diseases and how that predisposition may affect the selection of a specific therapy for patients with certain genotypes or how the information can be used to predict the outcome of a therapeutic intervention[3].

Role of gene variations in predicting drug response and drug development

From human genome project, many of the genetic variation have been found within human genome. These variations, or SNPs (single nucleotide polymorphisms), can be used as a diagnostic tool to predict a person's drug response. For this to happen, a person's DNA must be examined or sequenced for the presence of specific SNPs.

SNP screenings will benefit drug development and testing because pharmaceutical companies could exclude those people from clinical trials whose

pharmacogenomic screening would show that the drug being tested would be harmful or ineffective for them. Excluding these people will increase the chance that a drug will show useful to a particular population group and will thus increase the chance that the same drug will make it into the marketplace[1].

Importance of pharmacogenomics [2]

- ***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. Similarly, advance knowledge of particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapy.

- ***More powerful medicines***
  Pharmaceutical companies will create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will allow drug makers to produce a therapy more targeted to specific disease. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells.

- ***Better and safer drugs at the first prescription***
  Instead of standard trial and error method of matching patients with the right drugs, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy from the beginning. This will take not only the guesswork out of finding the right drug, it will speed recovery time and safety as the likelihood of adverse reactions is eliminated.

- ***More accurate methods of determining appropriate drug dosages***
  Current methods of dosages are based on weight and age that will be replaced with dosages based on person's genetics. This will maximize the therapy's value and decrease the likelihood of overdose.

- ***Better vaccines:***
  Vaccines made of genetic material, either DNA or RNA; promise all the benefits of existing vaccines without all the risks. They will activate the immune system but will be unable to cause infections. They will be inexpensive, stable, easy to store and capable of being engineered to carry several strains of a pathogen at once.

- ***Improvements in the drug discovery and approval process***
  Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug. Previously failed drug candidates may be revived as they are matched with the niche population they serve.

- ***Decrease in the overall cost of health care***
  Decrease in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get drug approved, the length of time patients are on medication, the number of medications patient must take to find an effective therapy, the effects of a disease on the body through early detection, and an increase in the range of possible drug targets will lead to a net decrease in the cost of health care.

Application of pharmacogenomics in various diseases

Pharmacogenomics has found its application in various diseases. Current knowledge of sporadic degenerative disorders or diseases suggests that, despite their multifactorial etiopathogenesis, genetics plays a primary role in describing the pathological events, and even dramatically changes the disease phenotype from patient to patient. Genes may act as susceptibility factors, increasing the risk of disease development, or may operate

as regulatory factors, modulating the magnitude and severity of pathogenic processes or the response to drug treatment. The goal of pharmacogenomics is the application of this knowledge to elaborate more specific and effective treatments and to tailor therapies to individual patients according to their genetic profile. In addition, polymorphism in drug metabolizing enzymes, drug transporters and receptors etc., is also one of the area of pharmacogenomics. There are many diseases for which pharmacogenomics has been described like, Parkinson disease, Alzheimer disease, rheumatoid arthritis and other inflammatory disease, breast cancer etc. Since it is not possible to describe all diseases at a time over here, only Alzheimer disease and breast cancer are mentioned here.

Pharmacogenomics of alzheimer disease

Alzheimer's disease is the most common type of dementia in the elderly. The neuropathological pathway of Alzheimer disease are large neuron loss along with neuritic plaques and neurofibrillary tangles, preferentially located in limbic and cortical areas of the brain[4,5]. Extensive loss of synapses occurs in the same regions of the brain affected by Alzheimer disease, with concomitant alterations of neurotransmitters systems[6,7]. Neuritic plaques are multicellular lesions containing extracellular deposits of β-amyloid protein. Neurofibrillary tangles are intraneuronal, cytoplasmic bundles of paired, helical filaments, composed of hyperphosphorylated, insoluble forms of microtubule associated protein, tau, which is often conjugated with ubiquitin [4].

Role of amyloid and its genetics

It is widely known that deposition of β-amyloid protein is the key event that leads to Alzheimer disease, derives from a precursor called as amyloid precursor protein which in neurons consists of 695 amino acid residues. In Alzheimer disease, processing of amyloid precursor protein is significantly altered and undergoes cleavage by various endoprotease namely α, β and γ secretase. Proof of genetic factors in the development of Alzheimer disease comes from epidemiological data. A family history of Alzheimer disease can be found in about 30% of patients, as indicated by the presence of at least one first-degree relative affected by the disease and concordance for Alzheimer disease in monozygotic twins is higher than in dyzygotic twins[8]. About half of the autosomal dominant inherited forms of Alzheimer disease feature an early onset of disease and are accounted for by mutations of the amyloid precursor protein, presenilin-1 (PS-1), or presenilin-2 (PS-2) gene. The gene of amyloid precursor protein maps on chromosome 21q21.2, and at least 7 different mutations are known to be the cause of early onset dominantly inherited Alzheimer disease. They are all missense mutations located at the level of α-, β-, or γ-secretase cleavage sites, altering the normal proteolysis of the amyloid precursor protein[9,10].

The PS-1 gene, whose function is not clearly known, locates on chromosome 14q24.3 and mutations in this gene are responsible for the majority of cases of autosomal dominantly inherited Alzheimer disease. More than 60 mutations of the PS-1 gene have been associated with early onset familial Alzheimer disease and almost all of them are missense mutations [9,10].

The PS-2 gene maps on chromosome 1q31-q42 and codes for a 448 amino acid protein sharing 67% sequence homology with PS-1 protein. Two missense mutations of the PS-2 gene have been identified to date and are associated with rare cases of early-onset familial Alzheimer disease[9]. The fundamental role played by presenilin genes in the pathogenesis of early-onset familial Alzheimer disease prompted investigations on their potential involvement in sporadic Alzheimer disease. Further investigation is needed for identification of specific polymorphisms of presenilin genes that are

associated with an increased risk of Alzheimer disease to account the preventive therapy as a major issue in asymptomatic individuals carrying these gene variations. Immunization with β-amyloid protein has found to prevent neuritic plaque formation and that peripheral administration of anti β-amyloid protein antibodies reduces neuritic plaque burden [10,11]. Trials in human are under process and if will be found safe, than β-amyloid protein may become the first line treatment for asymptomatic subjects with a high risk for Alzheimer disease. γ-secretase inhibitors are also under active investigation because they may provide the most direct pathogenetic treatment for patients with Alzheimer disease carrying mutations of the amyloid precursor protein, PS1, or PS2 gene[12].

Other genetic hypothesis includes apolipoprotein E (ApoE) gene, by analysing the allele polymorphism of the patients with late onset Alzheimer disease. The ApoE gene maps on chromosome 19q12-q13 and contains three common coding sequence polymorphisms named ε2, ε3 and ε4 allele. The ApoE ε4 allele has been associated with a higher risk of Alzheimer disease, may be due to its higher affinity for β-amyloid protein compared to other alleles and to its propensity to enhance the aggregation or reduce the clearance of β-amyloid protein[4].
Another single nucleotide polymorphism at position 491 in the 5'-promoter region of ApoE has been reported to be associated with an increased risk of Alzheimer disease[13]. These data need further clarification by other investigators.

Several other gene polymorphisms have also been associated with an increased risk of Alzheimer`s disease, which code for proteins, which may participate in β-amyloid protein processing or aggregation in neuritic plaques. α-1-antichymotrypsin is a protease inhibitor and an acute-phase protein also found in amyloid deposits in Alzheimer disease brains[14].

A polymorphism in the region coding for the signal peptide of the α-1-antichymotrypsin gene was originally reported to confer a higher risk of Alzheimer disease and that this effect is enhanced by a concomitant polymorphism of the interleukin 1βgene[15]. Therefore, polymorphism analysis of α-1-antichymotrypsin gene, especially in conjunction with that of the interleukin-1β gene, may provide further indications for the use of anti-inflammatory drugs or interleukin-1 receptor antagonist in Alzheimer disease[16].

α-2-Macroglobulin, another proteinase inhibitor, is detected in amyloid plaques and interacts with the lipoprotein receptor related protein (LRP) [9]. It also binds to β-amyloid protein and such complexes may be cleared through binding to LRP or deposition in amyloid plaques. A selective polymorphism near the 5' end of the α-2-Macroglobulin gene has been associated with an increased risk of Alzheimer disease and this may reflect a genetically determined defective removal of α-2-Macroglobulin/β-amyloid protein complexes[17].

LRP is a member of the low density lipoprotein receptor superfamily and is believed to contribute to the clearance of ApoE/β-amyloid protein and α-2-Macroglobulin/β-amyloid protein complexes[18]. The LRP gene was examined for DNA variations and a tetranucleotide repeat polymorphism in the 5' region was found to be associated with an increased risk of late-onset Alzheimer disease[19]. LRP is also a receptor for cholesterol and studies showed that a reduction in cholesterol levels by lovastatin and methyl-β-cyclodextrin inhibits the production of β-amyloid protein by cultured hippocampal neurons[20]. So, statins may be considered as a potential treatment for patients with Alzheimer disease carrying certain LRP genotypes. Further study in this direction is required.

Other gene polymorphisms have been reported to add to the risk of developing

Alzheimer disease includes VLDL receptor[21,22], tau protein[23], cathepsin D[24], bleomycin hydrolase[25]. However, further analysis on wider population is required before any definitive conclusions are drawn. Nonetheless, mutations or polymorphisms of some of these genes may suggest interesting and unexpected therapeutic approaches for genetically selected candidates.

Various genotypic variations and proposed corresponding therapies related to Alzheimer disease has been shown in table given below [51].

Pharmacogenomics of breast cancer

Breast cancer is one of the most common causes of cancer death in the developed world. It is spreading its threat the whole globe. Locally advanced or metastatic breast cancer is typically treated with chemotherapy. Multiple combinations of chemotherapy regimens are available, including anthracyclines, taxanes, antimetabolites, alkylating agents, platinum drugs and vinca alkaloids[26]. There are multiple treatment options for breast cancer. Pre-or post therapy surgical resection is commonly used. Radiation therapy typically follows surgery for early stage disease and shows a reduction of local recurrence by 26% after 5 years of follow-up. Other treatment options include Partial breast irradiation via intra operative radiotherapy, brachytherapy, or three dimensional conformal radiotherapy, is being assessed in clinical trials[27].

In postmenopausal women, oestrogen receptor and/or progesterone receptor positive breast cancer (approximately 70% of all postmenopausal breast cancer) are typically treated with anti oestrogen therapy. Tamoxifen has been the mainstay of endocrine therapy; which is a direct inhibitor of the oestrogen receptor. Recently aromatase inhibitors like letrozole, exemestane and anastrozole have been developed[28]. These block oestrogen synthesis by inhibiting aromatase enzyme (CYP19A1).

Targeted therapy including monoclonal antibodies is relatively new field. HER2 over expression/ERBB2 amplification typically occurs in approximately 30% of breast tumors and trastuzumab is given to these patients usually in combination with chemotherapy regimens. Bevacizumab (Avastin), that targets the vascular endothelial growth factor (VEGF) and inhibits tumor angiogenesis was recently approved (2008) for use in combination with paclitaxel to treat HER2 negative metastatic breast cancer [29,30].

Anti-mitotic like Taxanes (specifically Paclitaxel and Docetaxel) stabilize the microtubules by binding to sites on tubulin dimmers, blocking tread milling and preventing the continuation of cell division. There are multiple studies which focus on transporter and metabolism genes, while very little progress has been made towards identifying pharmacogenomic makers for taxanes response and/or toxicity. In breast cancer CYP1B1*3 was identified as a marker for progression free survival[31]. In a study of 89 breast cancer patients treated with Paclitaxel and Doxorubicin, a 21 gene signature, known as Oncotype Dx panel, was found significantly associated with complete response [32].

Table 1
Various genotypic and proposed corresponding therapies related to Alzhiermer`s disease.

Genotype variations and corresponding therapies	
Gene	**Therapeutic**
Amyloid protein precursor	Immunization with β-amyloid protein, Anti-β-amyloid protein antibodies, β- and γ-secretase inhibitors, α-secretase stimulators
Presenilin-1	Immunization with β-amyloid protein, Anti-amyloid β-protein antibodies, γ-secretase inhibitors
Interleukin-1α/β	Anti-inflammatory drugs (e.g., ibuprofen, cyclooxygenase-2 inhibitors), interleukin-1 receptor antagonist
α-1-Antichymotrypsin	Anti-inflammatory drugs (e.g., ibuprofen, cyclooxygenase-2 inhibitors), interleukin-1 receptor antagonist
Lipoprotein receptor related protein	Statins
Angiotensin converting enzyme-1	ACE inhibitors
Oestrogen receptor alpha	Estrogens
Neurotrophic factors or neurotrophics factor receptors	Exogenous or transfected neurotrophic factors (NGF, BNDF, IGF-1, Neotrofin, AIT-082)
Apoptosis-related genes	Antiapoptotic drugs, caspase inhibitors

Pharmacogenomic data for Vinorelbine is insufficient. Study in patients with small cell lung cancer identified an association with ABCB1and CYP family gene[33]. However, study in 25 patients with breast cancer no association with the said above genes was observed [34]. Thus data are conflicting and require study on large group of population.

Despite being in use for over 30 years, pharmacogenomics has not focused on cyclophosphamide. Recent study of 85 breast cancer patients determined that patients with CYP3A4*1B or CYP3A5*1 had significantly higher cyclophosphamide AUC, indicating poor metabolism and also survival was associated with these genotypes, suggesting variants in CYP3A genes as sources for inter individual pharmacokinetic variability [35]. Another study in 103 Japanese cancer patients found association between CYP2B6*6, higher clearance and shorter half life of cyclophosphamide. No association between CYP3A polymorphisms and cyclophosphamide pharmacokinetics were

observed in this study[36]. Thus validation of the findings of these studies is essential to identify the role of cytochrome pharmacogenomics on cyclophosphamide pharmacokinetics, outcome and toxicity.

Studies of genes involved in the 5-fluorouracil and Methotrexate pathways in breast cancer are minimal. In 1067 Asian breast cancer patients MTHFR 677C>T was associated with risk of death[37], and a tandem repeat polymorphism in the target for 5-fluorouracil, TYMS (TYMS TSER polymorphism), was associated with survival in 35 breast cancer patients treated with 5-flurouracil containing therapy. However, further study is require to confirm the data. In 135 breast cancer patients a polymorphism in carboxylesterase 2 (CES2-823>G) demonstrated significantly improved response to capecitabine, and also a longer time to progression than patients with wild type CES2 [38].

In 74 breast cancer patients receiving Gemcitabine, a haplotype containing two variants in RRM1 (2455A>G and 2464G>A) was significantly associated with reduced incidence of neutropenia [39]. Further study is warranted to confirm the data.

Anthracyclines (mainly Doxorubicin and Epirubicin) are commonly used for the treatment of postmenopausal breast cancer. It has been suggested that HER2 amplification is predictive of response from anthracycline containing therapy, however, it has also been postulated that the real marker is topoisomerase IIα (TOP2A), which is located close to HER2 on chromosome 17[40]. The carbonyl reductases, CBR1 and CBR3 are responsible for phase 1 metabolism of Doxorubicin. Polymorphisms in CBR1 and CBR3 were assessed in 101 Southwest Asian breast cancer patients receiving doxorubicin containing therapy. CBR311G>A was associated with altered doxorubicin pharmacokinetics, in addition to significantly improved tumor reduction [41]. No associations with CBR1 polymorphisms were observed.

The influx transporter, SLC22A16 was assessed in 62 Asian breast cancer patients. The 146A>G polymorphism was associated with significantly higher exposure to Doxorubicin and Doxorubicinol [42]. The clinical impact in terms of response and toxicity is unknown. All three studies highlighted here were performed on Asian population. The roles of pharmacogenomics in non-Asian populations remain unclear. It is therefore important to validate pharmacogenomics associations in multiple populations [43].

In case of Epirubicin, The NQO1*2 allele was found to be a predictive marker for response to Epirubicin in breast carcinoma cells in vitro, and also predicts survival in Epirubicin treated breast cancer patients, along with NQO1 556C>T[44].

The pharmacogenomics of platinum has not been widely studied in breast cancer. The majority of studies have performed in non-small cell lung cancer. A recent study in 85 breast cancer patients treated with Cyclophosphamide, Cisplatin and Carmustine showed a significant association with improved median survival in patients carrying GSTM1 gene deletion, although it is unclear if the effect was on the Carmustine or Cisplatin or both[35]. There is lack of comprehensive information on pharmacogenomics of platinum compounds.

Chemotherapy for breast cancer is usually given in combination. However, although the majority of pharmacogenomics studies are performed on samples from patients who have received combination therapy, the polymorphisms assessed are usually deemed specific to one of the drugs used in the combination. In most cases, monotherapy is used for in vitro studies to determine novel genome regions involved in chemosensitivety [44, 45] or to assess the functional role of genetic polymorphism. Currently very few studies in vitro or in vivo have assessed combination therapy as a whole. Further, pharmacokinetic and pharmacodynamic data of combination therapy could overlap and make either stronger or weaker

pharmacogenomic associations when drugs are used in combination.

A study based on DNA damage being a common result of most chemotherapeutics assessed polymorphisms in DNA repair enzymes and cell cycle regulators in 180 patients with primary invasive breast cancer. The patients had been treated with anthracycline and the CMF regimen. A significant association with XRCC1 R399Q and disease-free survival was observed in all patients, regardless of prior radiation therapy[46]. This is an important study which shows that pharmacogenomics markers can be applicable to combination chemotherapy.

Issues and challenges related to pharmacogenomics

Application of proper method for discovery of genetic variance and their future in pharmaceutical industry for providing better patients care as economic incentive will be a break through[48]. However, a lot of hurdles are yet to be overcome. Various issues lie ethical, social and legal issues need to be addressed.

Ethical Issues

The most important issue that concerns pharmacogenomics is privacy of the study subjects. Participants should be adequately informed that how their genetic material will be handled, what all tests may be done, how and by whom the data will be utilized, where the genetic material be stored and how secure the DNA blanks are. 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. Patent's family should be informed or not, is one point to be addressed further[48, 49].

Better pharmacological care means better life expectancy. It should also affordable to common man and not only to those who are rich. Ethics demand equality, and thus the cost of these pharmacogenomic techniques should be subsidized by the government. In developing countries where the portable food is more important issue, there is question whether pharmacogenomic techniques should be further processed or not. While in developed countries like U.S., where adverse drug reactions play major role for morbidity and hospitalization, a lot of which can be avoided if genetic profile is known and drugs given accordingly[48].The interests of pharmaceutical companies in financial gain demands great attention.

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 analyze that. What is the legal liability if that data if stolen or lost or made public? Who is responsible for the damages? What is the compensation? Etc. One viewpoint is that the study should be informed only about the particular condition being tested and the rest should not be disclosed, meaning, a person should not be told the future[48].

What is 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 which is good for company as only best fitted individuals will be there to improve success but a loss for person who may have to face unemployment and switch over to malpractices, or insurance cover is avoided[50].

Social Issues

The economic burden of a new therapeutic science will be borne by the society. Knowing the genotype of 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[49].

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 standard. Pharmacogenomic variations may lead to

opening up of some constitutional like those of getting some special incentives or minority status[48].

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. The final decision will be made by the patient only. However, the physician may help him in rational decision making. For example, a patient deficient to Thiopurine S Methyl

Transferase (TPMT) is likely to undergo myelosuppression with anticancer chemotherapy[48]. Such patients can be advised to undergo pharmacogenomics testing so as to predict outcome and alternatives.

Pharmacogenomics and diagnosis

The ultimate aim of pharmacogenomics is the discovery of highly effective novel therapies to reduce the cost of drug development, but this cannot be achieved without using highly accurate diagnostic tests. 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[50].

Barriers to pharmacogenomics progress [2]

Pharmacogenomics is a developing research area that is still in its infancy. Several barriers that will have to be overcome before many pharmacogenomics benefits can be realized, that includes:

- Complexity of finding gene variations that affect drug response

  Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C or G) in the genome sequence is altered. SNPs occur every 100 to 300 bases along the 3-billion-base human genome, therefore millions of SNPs must be identified and analyzed to determine their involvement (if any) in drug response. Further our knowledge is limited in terms of which genes are involved with each drug response. Since many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time consuming and complicated.

- Limited drug alternatives:
  Only one or two approved drugs may be available for treatment of a particular condition. If patients gene variations that prevent them using these drugs, they may be left without any alternatives for treatment.
- Financial loss for drug companies to make multiple alternative pharmacogenomic products:
  Most pharmaceutical companies have succeeded with their “one size fits all” approach to drug development. Since it costs hundreds of millions of dollars to bring a drug to market, will these companies be will to develop alternative drugs that serve only a small portion of the 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 t determine which drug is best suited to each patients. 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.

CONCLUSION

So far, pharmacogenomics looks good on paper, by viewing that it promises the tailor made medicines for individual patients by testing the genotypic variations of the patients and prescribing the most effective medicines to them by causing minimal or no adverse reaction. However the real situation is not as that simple as it seems on the paper. The identification of SNPs from almost three billion base long human genome is a complex process. Further, application of the pharmacogenomics in the drug makes it more complex. Further, application of the pharmacogenomic in the drug development process is going to be a costly affair. The interest of the pharmaceutical companies in developing the drug that, "one size fits some" rather than "one size fits all" also has to be discussed in detail. May be the companies have to change their strategies for development of drug, but question arise how? At this stage, without government support in terms of subsides and exemptions, it seems unclear. Also individualized medicine will give rise to various discrepancies and issues which has to be addressed by higher authorities before full application of pharmacogenomics is done. Also patient's affordability is the major issue. Further, the economic analysis of pharmacogenomics is yet to be done. Searching a specific population with a particular genotype in which a given new drug to be effective may be both frustrating and time consuming. In this way initial screening of individuals seems to be costly affair. Also, the need of diagnostic techniques to fine out the specific SNP cost effectively may be problematic. A focused pharmacogenomic test assays the minimum number of specific markers relevant for a particular drug decision. The expanded tests involve assaying wide range of markers to provide genetic information even if the immediate requirement for the same is not there. This diagnosis will be done by highly expensive instruments which will cost to the patients. Role of physician has to be discussed because physicians are the one show will diagnose the disease and prescribe medicines accordingly. For this, their knowledge has to be sound about genetics. Although, aim of pharmacogenomics is discovery of highly effective novel therapies to reduce the cost of drug development, the cost will increase indirectly, unless some better, cheaper and patient oriented ways are not found. Pharmacogenomics can be a boon for whole world, but it is still in its infancy. Before full application of this branch, various issues and technical difficulties have to be critically analyzed.

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