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PHARMACOGENOMICS

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ABSTRACT

Pharmacogenomics is defined as the study of genes and how an individual response is affected due to drugs. Pharmacogenomics is an emerging new branch with combination of both pharmacology (the branch of science that deals with study of drugs) as well as genomics (the branch of science that deals with study of genes) for development of effective doses and safe medications tailored according an individual patient genetic makeup. Human Genome Project is one of the crucial projects in which researchers are developing and learning relation in genes and its effect on the body's response to medications. Difference in genetic makeup provides difference in effectiveness of medication and in future to predict effectiveness of medication for an individual and to study existence of adverse drug reactions. Besides advancement in the field of science and technology till date pharmacogenomics hangs in infancy. There is limited use of pharmacogenomics, but still, novel approaches are under clinical trials. In near future, pharmacogenomics will enable development of tailor-made therapeutics for treating widespread health problems like neurodegenerative, cardiovascular disorders, HIV, cancer, asthma, etc.

KEYWORDS: Pharmacogenomics, Pharmacogenetics.

INTRODUCTION

Pharmacogenomics is the branch of science concerned with the identification of the genetic attributes of an individual that lead to variable responses to drugs. Interestingly, the science has evolved to also consider patterns of inherited alterations in defined populations, such as specific ethnicities, that account for variability in pharmacotherapeutic responses. For the purposes of this chapter, the term *pharmacogenomics* is used more generally to refer to

genetic polymorphisms that occur in a patient population—for instance, in an ethnic group—as opposed to individual patients Until recently, the ultimate goal of pharmacogenomics had been the development of prediction models to forecast debilitating adverse events in specific individuals and, more recently, across populations based on similarities in age, gender, or more commonly, race or ethnicity, as contrasted with the rest of the population. However, in spite of this newer usage, pharmacogenomics may predict the extreme deviation of some patients from predictable pharmacokinetic and pharmacodynamics responses: the idiosyncratic response. Pharmacogenomics seeks to identify patterns of genetic variation that are subsequently employed to guide the design of optimal medication regimens for individual patients. Historically the approach to drug therapy has been largely empiric and based on clinical studies that determined the maximally tolerated dose and reasonable toxicity in a narrowly defined population. This approach typically leads to the safe and effective administration of drugs for most individuals. However, with empiric therapy, inter individual (allotypic) variation in drug response occurs—with patient outcomes varying from a complete absence of therapeutic response to potentially life-threatening adverse drug reactions (ADRs).

Genetic differences may account in part for some of the well-documented variability in response to drug therapy. Obviously, many factors other than genetics—such as age, sex, other drugs administered, and underlying disease states—also contribute to variation in drug response. However, inherited differences in the metabolism and disposition of drugs and genetic polymorphisms in the targets of drug therapy (e.g., metabolizing enzymes or protein receptors) can have an even greater influence on the efficacy and toxicity of medications.[1,2,3]

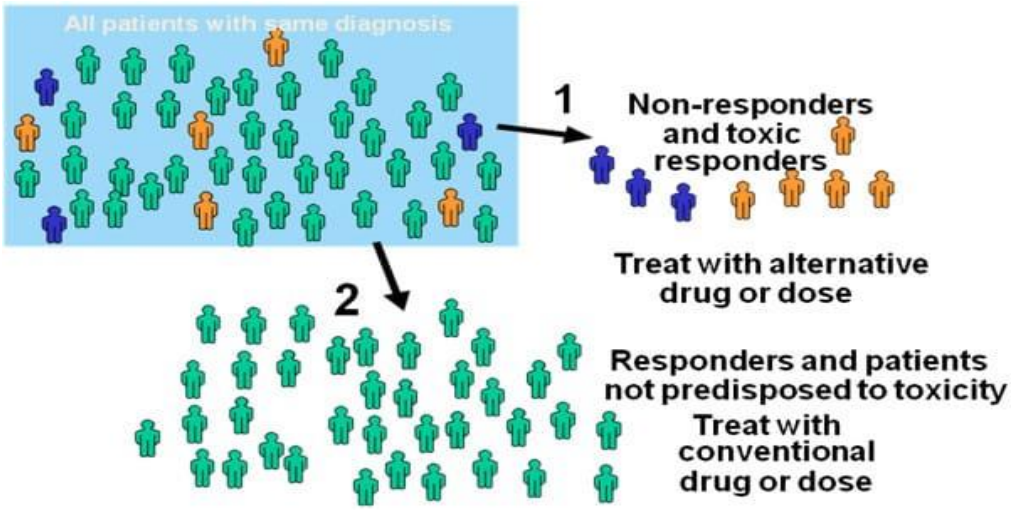

Fig. 1: Potential of Pharmacogenomic (49).

History

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bio informatic analyses in the 1970-1980s. The actual term 'genomics' is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) over beer at a meeting held in Maryland on the mapping of the human genome in1986.

In 1972, Walter Fiers and his team at the Laboratory of Molecular Biology of the University of Ghent (Ghent, Belgium) were the first to determine the sequence of a gene: the gene for Bacteriophage MS2 coat protein. In 1976, the team determined the complete nucleotide-sequence of bacteriophage MS2-RNA. The first DNA-based genome to be sequenced in its entirety was that of bacteriophage Φ-X174 (5,368 bp), sequenced by Frederick Sanger in 1977.[4,5]

The first free-living organism to be sequenced was that of Haemophilus influenza in 1995, and since then genomes are being sequenced at a rapid pace. A rough draft of the human genome was completed by the Human Genome Project in early 2001, creating much fanfare. As of September 2007, the complete sequence was known of about 1879 viruses, 577 bacterial species and roughly 23 eukaryote organisms, of which about half are fungi. Most of the bacteria whose genomes have been completely sequenced are problematic disease-causing agents, such as Haemophilus influenza. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms.[6,7]

PHARMACOGENOMICS

The ultimate promise of pharmacogenomics is the possibility that knowledge of the patient's DNA sequence might be used to enhance drug therapy to maximize efficacy, to target drugs only to those patients who are likely to respond, and to avoid ADRs. Increasing the number of patients who respond to a therapeutic regimen with a concomitant decrease in the incidence of ADRs is the promise of pharmacogenomic information. The long-term expected benefits of pharmacogenomics are selective and potent drugs, more accurate methods of determining appropriate drug dosages, advanced screening for disease, and a decrease in the overall cost to the health-care system in the United States caused by ineffective drug therapy.[3]

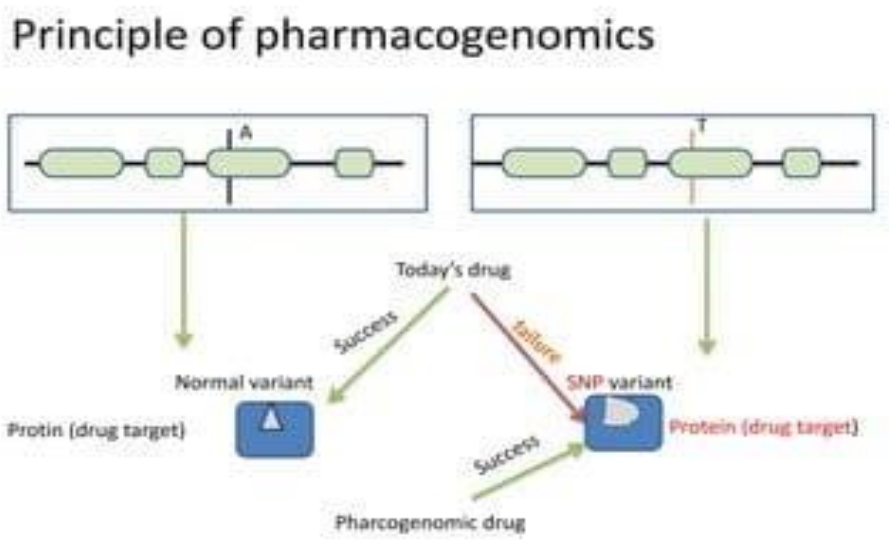

Fig. 2: Principle of Pharmacogenomics.[48]

Applications of Pharmacogenomics

Many common diseases having high morbidity as well as mortality rates have now known with well-established genetic components. The degree of role of genetics has been predicted for diseases like obesity and diabetes according to their sibling analysis.[13,14] In the same way, some rare gene mutations can provide a vision into the more complex biological processes.[15] For instance, when the subject possesses extreme levels of HDL in their blood, one can easily demonstrated the influence of CETP (cholesteryl ester transfer protein) on patients HDL levels.[16,17,18.]

In another case, a person having deactivating mutations due to the Janus kinase 3 (JAK 3) gene shows severe combination of immune-deficient syndrome, as sometimes inhibition of JAK3 was expected to affect the human immune suppression.[19,20] Hence, this led to a new investigation on drugs having CETP inhibition and JAK3 inhibition with the help of Pharmacogenetics.[21] Also, with the advent of pharmacogenomics, the path of relationships between disease state and human genes has now established which led to the suitable selection of therapeutic targets. Nowadays, many academic institutions and Pharmaceutical companies are moving toward the investigation on the relationship between disease phenotypes and genetic variations to better categorize diseases.[22,23] Although the collection of medical phenotypes having linkages with samples of DNA provides a prominent opportunity for examine the genetic variation which are present in patients. Investigation of genetic variation can be done by collection of DNA of particular patient. This is characterized

in a study where DNA from a person involves in trails of lipid lowering demonstrated a swift connection between phenotypic novel lipase gene family and for HDL levels. As per literature reports, above mentioned studies are based on a sound hypothesis which is linked to candidate's biological gene selection. Now it is easy to cross examine the genome selection which is solely depends on phenotypic criteria.[37,24] These stages have now substituted around 300,000 SNPs across the genome, by exploiting only few haplotype-defining SNPs. Perlegen sciences have developed newly genotyping technologies which has with a capability of genotyping mass hundreds or thousands of markers with the help of high-density based oligonucleotide arrays linked with restriction enzyme-based genomic reduction. However, as these technologies advances, still exact number of haplotype-defining SNPs is uncertain. Some findings are recently reported relation to assess polymorphisms across selected gene regions recommends that, it is necessary to reach an r2 of >0.8% in order to detect more than 80% of all haplotypes. Due to Hap Map project progression with defined LD patterns linkage, scientist working on genes will thorough assess to the degree of LD in a represented regions or selected regions. This will enable to explore more around selection of SNP regardless design of study.[25,26]

As genome approach does not depend upon selection of candidate genes, so understanding on complex diseases such as psychiatric or cardiovascular diseases will become more efficient. Some researchers believed that the new horizons on LD coverage about insights of human genome and SNP density will show the perception of a substantial genomic portion areas and its relation with interest of phenotype.[27,28] To assess the Perlegen Sciences chip-based array based platform and to justify the haplotype tagging approach for the identification of genetic associations, 7283 SNPs connecting 17.1 mega bases (Mb) of DNA were genotyped for detecting linkages with HDL levels. Further, SNPs were connected with 50 CETP haplo block gene were found out as the most valuable association in dataset. The companies like Perlegen and project like Hap Map project recently declared their purpose to provide it SNPs markers into public provinces to further advent to basis for such kind of experiments which help in the scientific community.[29,30]

Pharmacogenetics significantly expands the therapy outcomes and drug uses. Medications may prescribe in low dose under strict monitoring to patients which shows genetically predisposed to their adverse events. This would probably helpful for drugs having narrow therapeutic index such as warfarin may be started gradually in patients having VKORC1

genotype linked with improved warfarin sensitivity. With the help of Pharmacogenetics, it is now possible to reduce the number of subjects to conduct any experiment and chances of error may be eliminated for many diseases.[31,32]

On the contrary, clinicians may be able to minimize possible adverse effects with the aid of genetic information for matching suitable drug to suitable patient at an appropriate dose. For instances, traditional approach to the management of hypertension involves the trial of numerous anti-hypertensive drugs till the desired blood pressure achieved with adequate drug tolerability. In this case, few initial drugs/agents fail to produce lower blood pressure or shown intolerable adverse effects. This way of selection of drugs took long time which ultimately suffered by patients. On the contrary, Pharmacogenetics, based on the patients' DNA, offers the greatest response with the best tolerability of the drug. Based on genetic regulator of cellular functions, Pharmacogenetics may be able to produce new drugs with less adverse effects. For example, chromosome translocation and its derived enzymes are responsible for causing life-threatening chronic myeloid leukemia (CML) which led to accelerate FDA approval of inhibitor of translocation-created enzyme Imatinib.[33] In the end, this core subject improves the quality and cut down the total costs of healthcare by minimizing the number of adverse reaction and reduce treatment failures gives rise to the discovery of new genetic targets for disease management.[34,35,36]

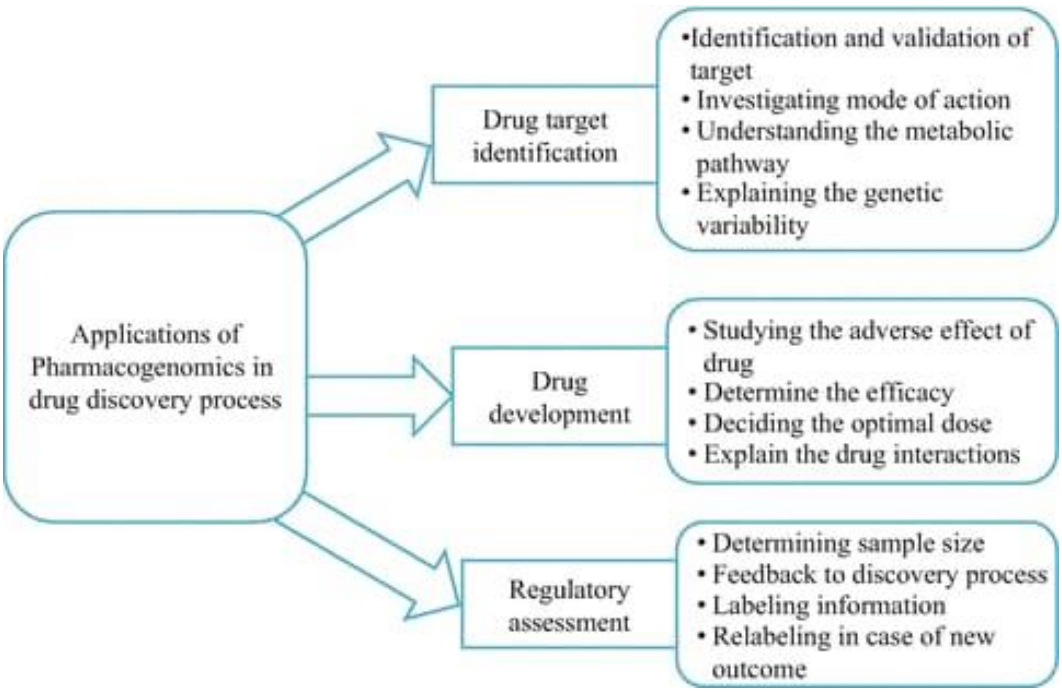

Fig. 3: Application of pharmacogenomics in drug discovery process.[47]

Benefits of pharmacogenomics

Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms. Following are the benefits.

Fig. 4: Benefits of pharmacogenomics.[50]

Pharmacogenomics in future

New developments in this field will impact on drug design at three main levels: the interaction of the drug with its receptor binding site; the absorption and distribution of the drug; the elimination of the drug from the body.[4,5,45]

Pharmacogenomics in Drug Discovery

Pharmacogenomics can impact how the pharmaceutical industry develops drugs, as early as the drug discovery process itself First, chem. informatics and pathway analysis can aid in the discovery of suitable gene targets, followed by small molecules as ‘‘leads’’ for potential drugs. Additionally, discovery of pharmacogenomic variants for the design of clinical trials can allow for safer, more successful passage of drugs through the pharmaceutical pipeline.

Applying Pharmacogenomic Knowledge

Pharmacogenomics has the potential to transform the way medicine is practiced, by replacing broad methods of screening and treatment with a more personalized approach that takes into account both clinical factors and the patient’s genetics.

As demonstrated previously, genetic variation can greatly influence the nature of the effects a drug will have on an individual (whether it will work or cause an adverse event), as well as

the amount of drug required to produce the desired effect. To this end, pharmacogenomics will impact the way drugs are prescribed, dosed, and monitored for adverse reactions.

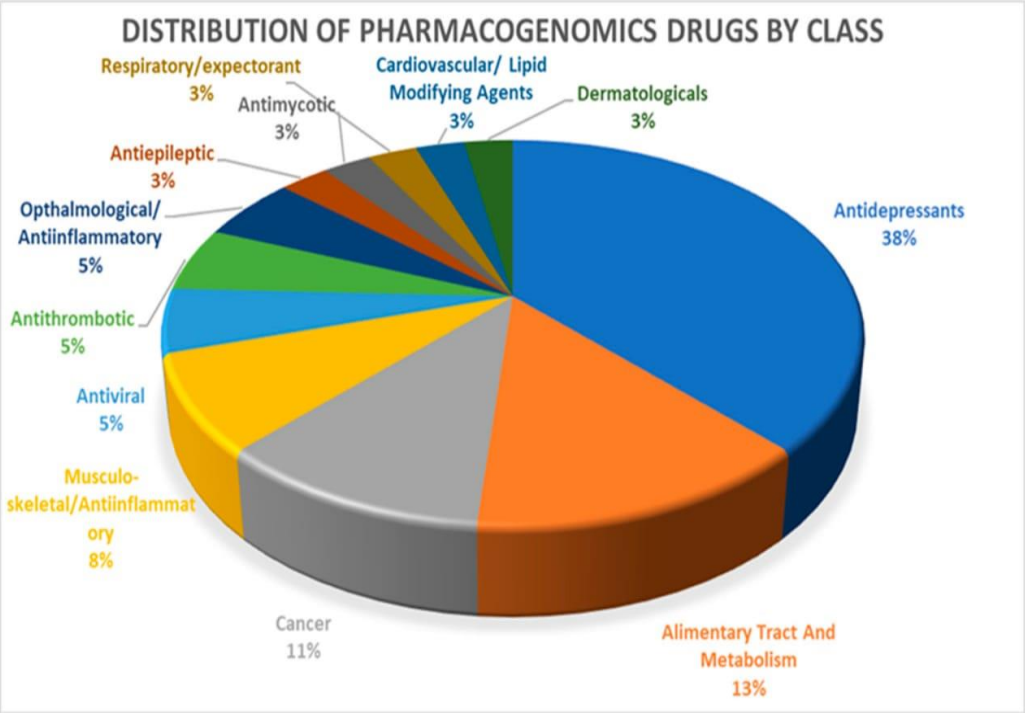

Fig. 5: Distribution of pharmacogenomics drugs by class.[51]

Clinical utility of pharmacogenomics

Strong evidence indicates that variants in about 20 genes affecting more than 60 drugs could affect one's response to these medications. Evidence-based, peer-reviewed guidelines are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (www.cpicpgx.org), an initiative funded by the US National Institutes of Health to help clinicians interpret the results of genomic tests and apply them to patient care.[8] Numerous examples for implementing pharmacogenomic testing have been published, with strategies ranging from preemptively testing everyone with panels of genes to testing single genes before prescribing certain drugs. But regardless of the implementation model, clinicians face challenges in deciphering the clinical evidence, and institutions face the challenge of creating the infrastructure to store genomic information that may be relevant throughout a patient's life.[9,10,11,12]

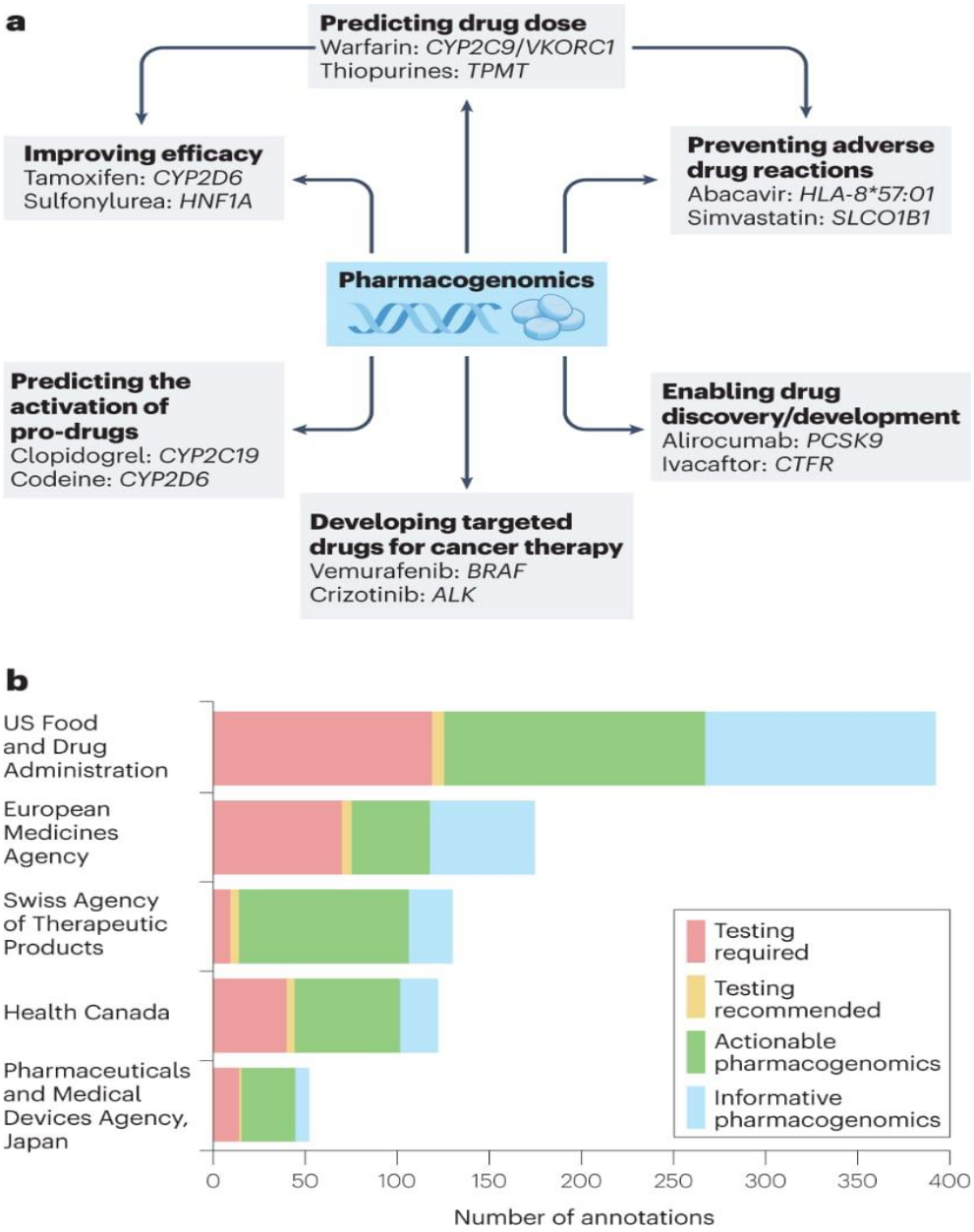

Fig. 6: Clinical utility by graphical representation.[52]

Barriers to pharmacogenomics progress

Pharmacogenomics is a developing research field that is still in its infancy. Several of the following barriers will have to be overcome before many pharmacogenomics benefits can be realized. They are the followings. **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 complicating of the process is our limited knowledge 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 have gene variations that prevent them using these drugs, they may be left without any alternatives for treatment.

Disincentives for drug companies to make multiple pharmacogenomic products

Most pharmaceutical companies have been successful 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 willing to develop alternative drugs that serve only a small portion of the population ?[46]

Addressing challenges to pharmacogenomic testing

Prospective, randomized clinical trials to assess the utility of pharmacogenomics can be difficult to carry out, particularly if testing for rare variants that would require a sample size of thousands to be sufficiently powered. Certain Pharmacogenetics variants are more or less common in different ethnic groups; it would be difficult for any study population to adequately reflect all ethnic groups, making the large number needed to power a trial to demonstrate clinical utility a significant limitation. Validity of clinical trial results may be limited by not testing for clinically important variants carried by the population being studied. Two randomized controlled trials for genotype-guided warfarin therapy illustrate this issue.

The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial compared fixed warfarin dosing vs genotype guided dosing and found better outcomes with genotype guidance. More than 90% of the study's participants identified as white.

The Clarification of Optimal Anticoagulation Through Genetics (COAG) trial compared patients who had warfarin dosage determined either by an algorithm based only on clinical variables or on clinical variables plus genotype data. In this trial, almost 30% of participants self-identified as black. Overall, no improvement in anticoagulation control was found, and in black patients, control was actually poorer in the genotype-guided group.

A possible explanation for the poorer control in black patients is that *CYP2C9* genotyping did not include decreased-function alleles (eg, *CYP2C9*8*) that are commonly found in patients of African ancestry. It is possible that the different dosing strategies between the 2 trials may have contributed to their opposite outcomes, suggesting that genotype-guided dosing may not be superior to algorithm-based dosing. The subsequent large Genetics Informatics Trial (GIFT) randomized elderly patients to either an algorithm based on clinical variables alone to guide warfarin dosing or one based on clinical variables plus *CYP2C9*, *CYP4F2*, and *VKORC1* genetic data. Similar to the EUPACT trial, this study's population was more than 90% white. The genotype-guided warfarin dosing arm had a reduction in the composite outcome of major bleeding, international normalized ratio greater than 4, venous thromboembolism, and death. These findings suggest that a genotype-guided algorithm is superior to a clinically guided algorithm when the appropriate genetic variants are included for the population being studied.[39,40,41,42]

Developing pharmacogenomic services

A few institutions are making efforts to incorporate preemptive pharmacogenomics testing, which can serve as models for their use. described implementing clinical pharmacogenomic testing of 3 gene drug pairs (*HLA-B*57:01*-abacavir, *HLAB** *15:02*-carbamazepine, and *TPMT*-thiopurines) in a large healthcare system. Custom rules and alerts were developed and integrated into the electronic health record to provide support for point-of-care decision-making. Such a system could be designed to also incorporate panel genotyping and triggering of clinical decision support alerts for those with an actionable genotype without further testing.

A pharmacogenomics clinic was also established consisting of medical geneticists, genetic counselors, and a pharmacist with specialized training in pharmacogenomics, who assessed the need for pharmacogenomic testing in individual patients and provided results and interpretation and medication recommendations. Patients were educated on the benefits, risks, limitations, and financial costs of pharmacogenomics before testing. Surgical services are conducting pilot studies to evaluate preemptive pharmacogenomic testing to better manage acute postoperative pain, reduce opioid consumption, and minimize recovery time after surgery. Compared overall benefit of analgesia scores and narcotic consumption in 2 groups: 50 patients who received pharmacogenomic-guided pain management after colorectal resection or major ventral hernia repair and a historical control group managed by an

enhanced recovery protocol. The pharmacogenomic-guided group had significantly lower scores (indicating better pain control) and consumed 50% less narcotics compared with the control group. Given that poor analgesia and adverse effects from medications may result in an unplanned admission to intensive care or lengthier hospital stays, preemptive pharmacogenomic testing could help minimize such events.[43,44]

Impact on pharmacy profession

Presently doctors diagnose and prescribe a drug on the trial and error basis and pharmacist advices about side effects and drug-drug interaction .But a day will come when you will take a gene report instead of blood reports .Thus after the diagnosis, pharmacist would interpret the panels of genetic results and advice you which drug would be best for your particular gene so that you have fast recovery.

CONCLUSIONS

Pharmacogenomics in pharmaceutical industry is a potential tool, awaiting use for the maximum benefit. It represents a radical advance in medical history. The main aim soft it are; personalized therapy, improvement in efficacy and reduction in adverse drug reactions, correlation of genotype with clinical genotype, identification of novel targets for new drugs, and Pharmacogenetics profiling of patients to predict disease susceptibility and drug response. In the past, most drugs were designed to work on the population level rather than being targeted for the individual patient. By reversing that trend, pharmacogenomics helps to refine the focus of treatment and makes drugs more effective and less toxic.

Rather than relying on the outward manifestation of disease the signs and symptoms that physicians call the phenotype – pharmacogenomic medicine examines and treats the genotype. Gradual inclusion of pharmacogenomic studies in drug discovery and development will cause substantial reduction in the expenses involved in drug development, ensure a safe clinical trial and reduce failures. Thus, many potential drugs which may be lost due to the effects on the outliers in a study can be retained when pharmacogenomic study is used in the future.

Individualized therapeutics or tailor-made therapy is one of the major goals of pharmacogenomics. In relation to inheritance other factors also contribute to individual therapeutics due to variation in response to administration of drug. Recently many developments in the field of pharmacology and genomics have made possible for physicians

to achieve individualization of therapeutics. These recent developments create possibility of thorough basis of particular drug for particular patient with motive of tailor-made therapy. Futuristic development in field of pharmacogenomics has paved the way to new emerging fields of pharma- coproteomic, pharmacotranscriptomics, and pharmacometabolomic. These new branches of science make it possible to achieve the concept of treat each patient as unique, complex, fascinating individual. At the end doubts about achieving individualized therapeutics with the help of this integrated system is still a dream in 21st century era.

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