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PHARMACOGENOMICS- A GENETIC APPROACH OF DRUG THERAPY

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Abstract:
Pharmacogenomics, the most prominent study being utilized in the medical sciences; leads to a better understanding of drug interaction. It is highly influential on the grounds of drug development and therapeutics. Its application in the field of drug development needs to be initiated on a large scale. It mainly drags attention towards the influence of genes and complex gene system in response to the drugs. New biomarkers have been discovered for easier identification of a group of patients who are less or more likely to respond to individual therapies, according to the recent workflow in the science of clinical therapeutics. It targets in improving personalized medicine, not just by right prescription but also delivering the right drug at the right dose at the right time.
Keywords: *Pharmacogenomics, Cardiology, Psychiatry.*

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INTRODUCTION: [1-8]

Pharmacogenomics is the study which deals with the genetic role of an individual in response to drugs. The pharmacogenomics term was first developed and used in 1990's. Before that, the word pharmacogenetics is used as a relevant term. An influence of acquired and inherited genetic variation is seen as a response to the drug in both pharmacokinetic and pharmacodynamic aspects. It helps to enhance drug therapy, with respect to the genotype of an individual and also to improve the maximum efficacy of the drug with lower adverse effects. The different patients will respond in a different manner even though the medication is same. These differences are more when we see among the huge population than compared to that of the same individual at different times. There are many nongenetic characters that influence the drug response activity such as age, sex, weight, organ function etc., there are also some genetic characters which influence and affect the drug response in the body. It helps to find out and discover new techniques for better functioning of drug and their approach towards the targeted sites. With the help of genotypes, we can find out which drugs are suitable for better responding activity in an individual. This genomics has brought up an approach for biological research for identification of genes and their response towards the drugs. It also helps researchers in mapping out the susceptibility of genes for multifactorial diseases. Gallaxo Wellcome has announced in 1999 about the identification of novel disease genes using this approach. And this type of approach will help in improving the genotypic technology. Clinical observations are documented about the inheritic differences of drug response for the first time in 1950's. Earlier there is a belief of applying same medication and one single dose for all the individuals but now we can develop a hope that by introducing pharmacogenomics, the older belief may get changed.

About 1.4 million single-nucleotide polymorphisms were identified in the initial sequencing of the human genome and then in the coding region, 60,000 of genes were identified. In these single nucleotide polymorphisms, some of them were associated with several consequential changes in a process of medication as a response to the drug. And some are still being processed for predicting the clinical response of the drug. For the patients who are unable to get therapeutic activity by the treatment can try alternate treatments related to pharmacogenomics. Some of the inputs used in the pharmacogenomics are genotyping, genome sequencing etc. The sequencing will give more data and also helps in detection of mutations which are carried on DNA strands by the genes. There is also another technique used for identification of targeted genes, that is by using of cDNA micro arrays which helps in detecting the activity, expression of a gene in disease or in normal stage. These techniques help in finding out the altered or effected DNA sequence during the diseased condition when compared with normal condition.

Description: [9-25]

Not only Drug-drug interactions and surroundings influences differences in drug response and disposition among individuals, genetic factors like inherited difference of drug targets, enzyme-metabolizing drugs and/or drug transporters also have equal importance. Thus, for prospective identification of patients who are at the risk for severe toxicity and also those who mostly benefit from typical treatment regimen, qualitative understanding of chemotherapeutic response related genetic determinants is required. The discovery of new targets from clinical trials, cost and timeline reduction in clinical trials, including and excluding selective patients by genotype, increasing efficiency in the drug discovery process by screening targets for variation, isolation of patients with the possibility of developing side effects from drug treatment, differentiation of the products, or the testing out of scientific hypotheses about the mode of action of the drug are mainly the aim of pharmacogenomics, from the perspective of pharmaceutical companies. Increased chances of the prescribed drug to successfully alleviate the diseases and reduced chances of dangerous Side Adverse Drug Reactions (ADRs) are the aim of pharmacogenomics from the patients' perspective. In clinical trials of 14 major drug categories, between 20% and 75% of the population derived no clinical benefit; showing drugs which are highly effective in most individuals demonstrate some inter-individual variations.

During the WW II, doctors observed that African-American soldiers treated with anti-malarial drugs were more likely to develop Haemolytic anaemia than their Caucasian colleagues. The basis was discovered in 1956.The cause was found to be mutations in G6PD (Glucose-6-Phosphate Dehydrogenase) gene.G6PD is required for reduction reactions which maintains red blood cells' integrity;

which is deficient in approx. 10% of African-Americans, thus, are greatly at risk of developing haemolytic anaemia when oxidant drugs (primaquine and other anti-malarial drugs) are administered. At molecular level, there are at least 10 different genotypes which result in the fast and slow inactivator phenotypes, and affect reactions to many therapeutic drugs and may also be related with susceptibility to different types of cancer.

Pharmacogenomics leads to a straight forward thought of improving the choice of drug for treating a given subject by considering the genetic make-up of the patients; unfortunately the threatening complexes would not allow this to happen so easily. However, there are some partial settlements. For instance, abnormal effects of a particular drug, known to be metabolized by a genetically variable enzyme, can be avoided by pretesting this enzyme in the patient and by giving the drug only when the patient's enzyme activity is normal or by reducing the drug dose if the activity is low. This kind of pretesting is not done when the drug is generally known to be safe and not to produce adverse effects. Thus, this process is not included in clinical routine.

The regulatory agencies in the U.S., Europe and Asia (i.e., FDA, EU-EMA and PMDA) have approved more than 1200 individual molecular entities. But, only a subset of about 15% of EU-EMA and US-FDA approved medications, containing pharmacogenomics information in their label, are deemed actionable. The information is shown in the below figure in the form of pie chart.
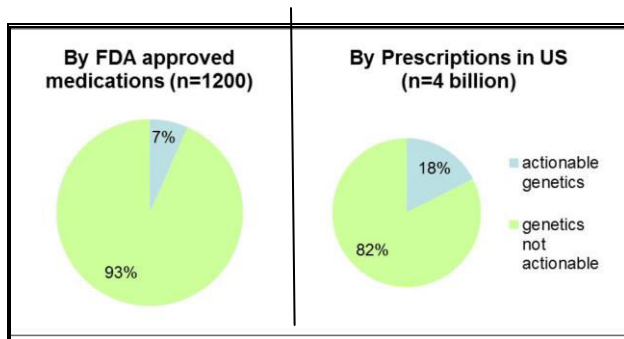

Figure 1: Pie chart describing about the medications in US.

The above figure shows nearly 18% of US outpatients prescriptions are affected by actionable

germline pharmacogenomics, whereas approximately 7% of FDA approved medications are affected by actionable inherited pharmacogenes, showing several pharmacogenetically high-risk drugs are commonly prescribed.

So far, only 17 of ~18,000 human genes are considered clinically actionable for germline pharmacogenomics. Moreover, most human germline genetic variations are unlikely to be actionable for medication. Also, pharmacogenomics is unlikely to be useful for improving prescribing for the majority of drugs. But, prescribing could be improved and outcomes optimized for that relatively small set of medications, if genetic testing were more widely and approximately deployed clinically. Along with which the number of such actionable gene drug pairs continues to grow, undeniably at a relatively slow pace.

Somatically acquired genomic variants that are specific to cancer tissues, is considered as a special case of pharmacogenomics. In some types of cancer, the guide of for the choice of anticancer agents can be somatic genomic variations, by virtue of identifying which malignancies are more or less likely to respond to specific anticancer agents. The recognition that cancer tissue can be differentiated from normal host tissue by the presence of genomic abnormalities like unfavourable ploidy in neuroblastoma, and cytogenetic abnormalities in acute lymphoblastic leukaemia, being used to determine the composition and aggressive of cytotoxic chemotherapy. The genetic testing of malignancies has become more specific in the recent years, as several anticancer drugs have been developed that are directed against or proven to be much more effective for tumors that harbour specific genetic variants, shown in the Table 1.

Table 1: Actionable somatic genome variants in associated medications and cancer cells:

Genetic Abnormality	HGVS	Target	Medications	Disease
AKT Mut (Act)	p.Glu17Lys	mTOR	sirolimus, everolimus	RCC
BCR-ABL (SV)	t(9;22) (q34.1;q11.21)	ABL	imatinib, dasatinib	CML, Ph+ ALL
BCR-ABL (SV + Mut)	p.Val299Leu	ABL	bosutinib, nilotinib	imatinib resistant CML
BCR-ABL (T135I)	p.Thr135Ile	ABL	ponatinib	CML, Ph+ ALL
BCR-ABL (SV)	t(9;22) (q34.1;q11.21)	SRC	dasatinib	CML, Ph+ ALL
BRCA1/2 variants	too numerous to list	PARP	olaparib	ovarian
BRAF SNVs (V600E/K)	p.Val600Glu, p.Val600Lys, p.Val600Asp	BRAF	dabrafenib, vemurafenib	melanoma
BRAF SNVs (V600)	p.Val600Glu, p.Val600Lys, p.Val600Asp	MEK	trametinib	melanoma
EGFR (Ex 19 del., SNV L858R)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	afatinib, erlotinib	NSCLC (EGRF+)
EGFR Mut (Act, Amp)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	gefitinib	NSCLC (EGRF+)
EGFR+ & WT KRAS	NA	EGFR	cetuximab, panitumumab	EGRF+ colon (WT *KRAS*)
EML-ALK (SV)	inv(2)(p21p23)	ALK	crizotinib	NSCLC
FLT3 CNV (Amp)	p.D600_L601insFREYEYD, p.Asp835Tyr	FTL3	sunitinib, sorafenib	AML
HER2 (Amp)	NA	ERBB2	lapatinib, trastuzumab	HER2+ breast
KIT (Act Mut)	p.Trp557_Lys558del, p.Asp579del, p.Val559Asp	KIT	imatinib, sunitinib	RCC, GIST
PDGFR (Mut, SV)	p.Asp842Val	PDGFR	sunitinib, imatinib	RCC, GIST, pancreas
PI3K (Mut, Amp)	PIK3CA p.Glu542Lys, p.Glu545Lys; p.His1047Arg, p.His1047Leu	PI3K	idelalisib	CLL, NHL
RARA (SV, gene fusion)	t(15;17)(q24;q21)	RARA	tretinoin, alitretinoin	APL CTCL, Kaposi
RARA (SV, gene fusion)	t(15;17)(q24;q21)	RARA	arsenic trioxide	APL
SMO (Mut, Act)	p.Trp535Leu, p.Arg199Trp, p.Arg562Gln	Smoothen	vismodegib	basal cell
VHL (Mut)	too numerous to list	VEGFR	sorafenib	RCC, hepatic, thyroid

Abbreviations for the terms used in the above table:

- Medications targeting normal cell surface proteins that are expressed on some tumor cells (e.g., ER, PR, CD20, CD30, CD52) are not included in this summary of drugs targeting proteins with aberrant expression or function due to somatic genome variants.
- Act= activating; Amp= amplification, typically by CNV; CNV=copy number variant; Epigen= epigenetic; Mut=mutation; NA = not applicable; SNV= single nucleotide variant; SV= structural variant.
- Only representative examples of known mutations are shown.
- Targets are generally protein products encoded by the gene listed.
- ALCL= anaplastic large cell lymphoma; ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; CLL=chronic myeloid leukemia, CML= chronic myeloid leukemia; CTCL= cutaneous T-cell lymphoma; Ex= exon; GIST= gastrointestinal stromal tumor; NHL= non-Hodgkins lymphoma; NSCLC= non-small cell lung cancer; RCC= renal cell carcinoma.

Applications: [26-28]

- It helps in maintaining and improving safety measurement of drug
- It helps in identification of gene expression by which it helps in determining the diseased or altered state of the gene when compared to the normal gene of an individual.
- It helps in identifying genetic predisposition and optimal dosing of the drug.
- It helps in discovering a new drug therapy targeted to human disease.
- It helps in increasing the rate of efficacy of the drug.

Pharmacogenomics is also applied in different streams of medicine like Cardiology, Psychiatry and Oncology etc. In recent times it has also become an important aspect of forensic technology, especially forensic pathology.

Pharmacogenomics in Cardiology: [29-32]
Now a day's cardiovascular problem are becoming primary cause for death in most of the developing countries. So for cardiac-related diseases different cardiovascular drugs are prescribed for the treatment.

These drugs show their response depending on some of the factors such as age, sex, gender, diet, concominent drug use and some of the environmental factors. So according to this factors, the drug therapy and response is varied from one individual to other. Even though these drugs are prescribed according to these factors, still there might be a chance of variation. These variations are due to the genetic influence on the drug. So pharmacogenomics helps in concentrating on genetic determinants which are responding to the drugs and it helps in avoiding the adverse effects of it and improves the effectiveness of the drug. Generally anticoagulants', antihypertensive drugs, platelet aggregation inhibitors etc. are used in cardiovascular treatment. In this pharmacogenomics treatment, polymorphisms in genes are carried out so that it helps in encoding the target sites of the drugs and enhance the activity and effectiveness of the drug. CytochromeP450(CYP) enzymes are the genes involved in the metabolism of the drug. And these enzymes are classified under pharmacokinetic genes. Cytochrome2C19(CYP) enzyme is also used for preventing the reduction in plasma concentrations, decrease in inhibition of platelet aggregation and adverse cardiovascular events. Especially it helps in the treatment of acute coronary syndrome and percutaneous coronary intervention (PCI).

Pharmacogenomics in Psychiatry: [33-35]
Pharmacogenomics is also applied in the treatment of several psychiatric disorders. Generally, cytochromeP450 is involved in pharmacokinetic aspects of the drug. The enzyme cytochrome2D6 is used in metabolizing the drugs related to antidepressants and antipsychotics. And this metabolizing action of enzymes is varied in to poor, intermediate, extensive and ultra rapid. Poorly metabolizing action can be detected by genotyping 5-10 nucleotide polymorphisms. In the case of ultra-rapid metabolizing enzymes it is partly predicted by the process of genotyping. By this genotyping, we can identify the frequencies of the gene so that variation and adverse reaction of the gene is identified. Cytochrome2D6 enzymes of poorly metabolizing activity have higher responding rates when compared with the extensive metabolizers. Cytochrome2B6 is also used for high polymorphic activity but due to some strong regulation by ligand activated nuclear receptors, in contrast to

cytochrome2D6 and may be involved in metabolizing activity. Some of the drugs like atomoxetine and methadone are used for the antipsychotic activity. The enzymes cytochromeP2B6 and cytochromeP3A4 are used as metabolizers in methadone treatment. Among the genes involved in pharmacokinetics, the members of the cytochrome P450 (CYP) family display large interindividual and interethnic variability in activity.

Pharmacogenomics in warfarin: [36-40]

Warfarin is one of the most widely used anti-coagulants, which acts by reducing the activity of vitamin-K dependent clotting factor. Warfarin is used in the prevention and treatment of thrombosis venous, pulmonary embolism, and other complications that are associated with atrial fibrillation and cardiac valve replacement. Sometimes warfarin is also prescribed to reduce the risk of stroke after myocardial infarction. Warfarin inhibits the enzyme encoded by VKORC1, which catalyzes the conversion of vitamin K epoxide to the active reduced form of vitamin K, vitamin K hydroquinone. It's an essential cofactor in the synthesis of various clotting factors. If there is a low availability of vitamin K hydroquinone then it leads to decreased activity of the clotting factors II, VII, IX and X and the anticoagulant proteins C and S.

Warfarin tablet contains a racemic mixture of R-isomer and S-isomer. 70% of warfarin's anti-coagulant effect is due to S-isomer. S-warfarin is mainly metabolised by CYP2C9, while R-warfarin is metabolised by CYP3A4 along with the involvement of several other cytochrome P450 enzymes.CYP29C and VKORC1 genotypes of the patient can be used to determine the optimal starting dose of warfarin. The CYP450 genes are polymorphic and can also result in reduced, increased or no enzyme activity. It's a diverse group of enzymes that form a major system for metabolising the lipids, hormones and the drugs in the liver. The isoenzymes of CYP450 are involved in the metabolism of warfarin that includes CYP2C9 and CYP3A4. The CYP2C9 is a wild allele and is associated with normal enzyme activity and normal metabolizing activity. VKORC1 gene encodes vitamin K epoxide reductase enzyme. It catalyzes the rate-limiting step in vitamin K recycling. It is the target of the drug warfarin. Missense mutations in VKORC1 can lead to warfarin resistance.

Somatic mutations in cancer pharmacogenomics: [41-45]

Mutations that occur spontaneously accumulate in the somatic cells throughout a persons' life. Most of these mutations do not have any visible effects, but few can alter the key cellular functions. Somatic mutations at the early stage can cause developmental disorders but the continuous accumulation of mutations can lead to cancer. The origins of human cancers remain uncertain except for a limited number of potent environmental mutagens, such as tobacco and UV light, and in rare cases, familial germline mutations that affect tumor suppressor genes or oncogenes. A significant component of cancer etiology has been deemed stochastic and correlated with the number of stem cells in a tissue, the number of times the stem cells divide and a low incidence of random DNA polymerase errors that occur during each cell division. While somatic mutations occur during each round of DNA replication, mutations in cancer driver genes are not stochastic. Out of a total of 2843 codons, 1031 can be changed to stop codons by a single base substitution in the tumor suppressor APC gene, which is mutated in 76% of colorectal cancers (CRC). However, the nonsense mutations, which comprise 65% of all the APC driver mutations in CRC, are not random: 43% occur at Arg CGA codons, although they represent <3% of the codons. In TP53, CGA codons comprise <3% of the total 393 codons but they account for 72% and 39% of the mutations in CRC and ovarian cancer OVC, respectively. This mutation pattern is consistent with kinetically slow, but not stochastic. Hydrolytic deamination of 5-methylcytosine residues at specific methylated CpG sites to afford T·G mismatches that lead to $C \rightarrow T$ transitions and stop codons at CGA. Analysis of nonsense mutations in CRC, OVC and a number of other cancers indicates the need to expand the predictable risk factors for cancer to include, in addition to random polymerase errors, the methylation status of gene body CGA codons in tumor suppressor genes a-tR.

CONCLUSION:

Pharmacogenomics is a potential tool in the pharmaceutical industry. It represents a radical advancement in medical history. It mainly aims towards; 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 pharmacogenetic profiling of patients to predict disease susceptibility and drug response. Earlier,

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 focus on the treatment and making the drugs more effective and less toxic. Rather than relying on the outward manifestation of the disease, the signs, and symptoms that physicians call the phenotype pharmacogenomic medicine examines and treats the genotype. Gradual inclusions of pharmacogenomic studies in drug discovery and development will cause a substantial reduction in the expense that are involved in drug development, ensures a safe clinical trial and reduced failures. Thus, many potential drugs which may be lost due to the effects on the outliers in a study can be retained when the pharmacogenomic study is used in the future.

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