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Recent Advance Study on Pharmacogenomics: A REVIEW

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Abstract: Pharmacogenomics can enhance patient care by optimizing pharmacological selection and administration, minimizing the risk of side effects, and increasing patient and provider satisfaction. Over the last 10 years, genetic testing technology has advanced, and clinical evidence supporting pharmacogenomics' incorporation into clinical practice has gotten stronger. Pharmacogenomics is the application of genome-wide techniques to understand how genes influence drug response and to develop novel drugs. Pharmacogenomics is the study of how human gene information impacts medication response, with the goal of increasing efficacy while minimizing negative effects. The ultimate goal of pharmacogenomics is the belief that patients' DNA sequences may be utilized to enhance disease treatment therapy in order to optimize efficacy, target pharmaceuticals only to those who are likely to respond, and reduce adverse drug reactions (ADRs). This article provides an overview of pharmacogenomics research, which aims to identify the genes (and gene variants) responsible for a drug's interactions with the body.

Keywords: Pharmacogenomics, Side effect, Medicines, Gene, Safety.

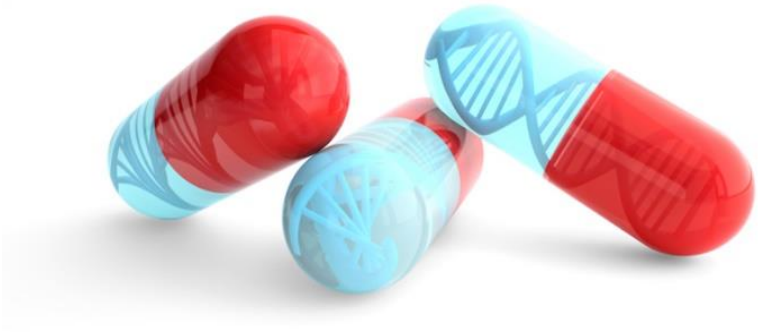
I. INTRODUCTION

What is pharmacogenomics?

Pharmacogenomics, often known as pharmacogenetics, is the study of how any person's genes impact or how gene reacts to drugs. Pharmacogenomics' long-standing goal is to aid medical practitioners in selecting the appropriate drugs and doses for individual patient. It comes under the concept of precision medicine, having the aims to treat each patient individually in order to decrease side effects and maximize efficacy. 1

It is estimated that more than 90% of individuals worldwide have at least one genetic variation that should require a change in dosage or treatment if a patient is prescribed a particular prescription. 2

An efficient and potentially money-saving risk-mitigation strategy may include using pharmacogenomics as a clinical tool to direct physician about the drug selection and dosage modifications.3



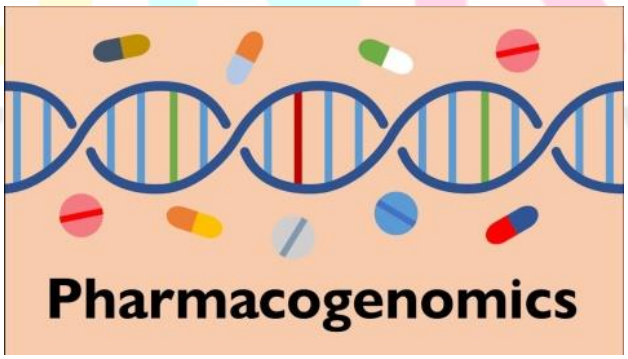
Pharmacogenetic parameters can also contribute to serious adverse drug reactions and there have been several publications detailing the number of drug related fatalities and hospitalisations, the causes of which may have a genetic basis [4, 5]

There are several reasons for medication response variability. inability to target the underlying illness mechanism through adequate pharmacological therapy, drug interactions, disease-related changes in drug concentrations or responsiveness, poor compliance, and system faults such as inability to deliver the correct medicine or dose to the patient are frequently noted. In some cases, treatment non-responsiveness and ADRs differ by race/ethnicity and can lead to clinical outcome discrepancies. To address such issues, pharmacogenomics research is required.[6]

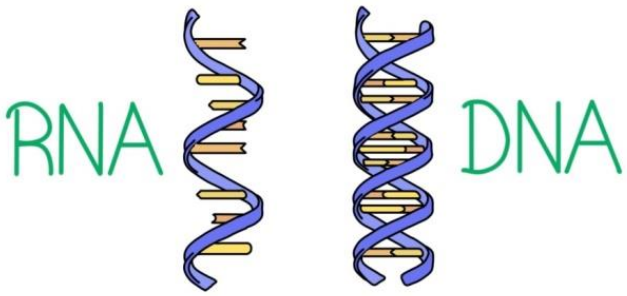
Pharmacology expertise in relation to pharmacogenomics: Pharmacogenomics of treatment response combines genetic information with pharmacokinetic and pharmacodynamic (what the body does to a medicine) effects.7 in general, the interaction between pharmacokinetics and Pharmacodynamic procedures.

The pharmacokinetics hypothesis states that a drug's interactions with proteins influence the processes of absorption, distribution, metabolism, and excretion (ADME). These variables influence how soon a drug reaches its target and how long it remains active. Before a drug can be provided, it must be absorbed by the body and carried to the appropriate organs and cells.8 Oral delivery of a tablet or capsule may be partially absorbed or destroyed before reaching systemic circulation, but intravenous administration ensures 100% bioavailability. The ability of a medicine to disperse (or reach its target) after entering systemic circulation is reliant on molecular transport difficulties. Absorption can be influenced by genetic variations in the proteins that mediate these processes..[9]

Pharmacodynamics (PD) records the precise influence of the treatment on its targets and downstream pathways, as opposed to pharmacodynamic interactions. Drug-target interactions can be either "on-target," where they have a beneficial effect, or "off-target," where they have a negative impact. Furthermore, PD studies how a drug concentration impacts the target, such as the concentration necessary to have the highest effect, the point at which more drug has no further effect on response, and the concentration required to get half of the maximum effect[10]



II. KNOWLEDGE OF GENE CONSIDERATION PHARMACOGENOMICS:



DNA, also known as deoxyribonucleic acid, is the genetic information carrier in humans and nearly all other organisms. DNA may be present in practically every cell in a person's body. While the majority of DNA is located in the cell nucleus (referred to as nuclear DNA), a small amount is also present in the mitochondria. This DNA is referred to as mitochondrial DNA (mtDNA). Dietary energy is converted into a form that cells can use by mitochondria, which are cellular organelles. The nitrogenous bases cytosine (C), guanine (G), adenine (A), and thymine (T) are found in DNA.[11]

Both polynucleotide strands must create hydrogen bonds with complimentary bases in order to remain connected. Adenine (A) is associated with thymine (T), whereas cytosine (C) is associated with guanine (G). Each thread complements the others in this way. A double helix is formed by twisting two polynucleotide strands together. Because each strand of the double helix runs in the opposite direction, the two strands are antiparallel. The strand's asymmetric endpoints are the 5' and 3' ends. The double helix features main grooves that are 22 A wide and minor grooves that are 12 A wide.[12]

Adenine (A), guanine (G), cytosine (C), and thymine (T) are the four chemical bases used to store data in DNA. The nearly 3 billion bases that make human DNA are shared by over 99% of the population, resulting in a rather homogenous group. The arrangement, or sequence, of these bases influences the information available for an organism's development and maintenance, much as how the letters of the alphabet appear in a certain order to make words and sentences. DNA base pairs are formed when the nucleotides A and T are joined together. Each base also has a phosphate and sugar molecule connected to it. A nucleotide is composed of a base, a sugar, and a phosphate. The double helix is made up of two long nucleotide strands that spiral togetherThe base pairs are the rungs of the double helix-shaped ladder, while the vertical side rails are sugar and phosphate molecules. The capacity of DNA to replicate, or make duplicates of itself, is a critical characteristic. The blueprint for repeating the base sequence is contained in each of the double helix's two DNA strands. This is crucial because, as cells divide, each new cell requires an exact replica of the DNA from the previous cell. A double helix is formed by the base pairs that link DNA's sugar-phosphate backbone. UV rays have the ability to harm DNA.develop. [13]

The bulk of RNA, also known as ribonucleic acid, is present in the cytoplasm. Some could even be discovered in the nucleus. Viruses commonly employ RNA genomes to store their genetic material. RNA is important in the control and expression of genes. RNA, like DNA, is a polynucleotide composed of nucleotide monomers. The strand of RNA is much shorter than the strand of DNA. Ribose is the sugar found in the sugar-phosphate backbone. Ribose is highly reactive due to the presence of hydroxyl groups at two distinct places on the pentose ring. RNA is not stable in a very alkaline environment. Because of the two little grooves. Nitrogenous bases present in RNA include cytosine (C), guanine (G), adenine (A), and uracil (U). Unlike DNA, RNA is primarily a single-stranded molecule that may generate double-stranded secondary structures such as hairpin loops by coupling complementary nucleotides. Adenine (A) and uracil (U) combine, whereas cytosine (C) and guanine (G) combine. The majority of functional forms of RNA contain tertiary structure. Messenger RNA (mRNA), transfer RNA (IRNA), ribosomal RNA

(rRNA), small nuclear RNA (snRNA), and other non-coding RNA (ncRNA) kinds are the main physiologically active RNA types. Protein synthesis is linked to mRNA, tRNA, and TRNA. ncRNA has a role in gene regulation and RNA processing. RNA polymerase is the enzyme that catalyzes the reaction where RNA is not easily damaged by ultraviolet radiation.[14]

Genetic testing:

A variety of genetic tests can be performed to examine chromosomal, gene, or protein alterations. When deciding on the right test, a doctor will evaluate a variety of aspects, including the suspected sickness or illnesses and the genetic defects that are usually connected with such problems. If the diagnosis is unclear, a test that turns off several genes and chromosomes may be used. However, if a specific ailment is suspected, a more specific test may be performed.

III. GENETIC TESTING PROCEDURE:

After a patient has decided to proceed with genetic analysis, a medical professional can arrange for testing. A genetic consultation frequently includes genetic testing. In genetic testing, several tissues such as blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), and amniotic fluid samples are utilized. A buccal smear method, for example, uses a small brush or cotton swab to collect a sample of cells from the inner surface of the cheek. Depending on the suspected disease, the sample is sent to a lab where experts look for particular abnormalities in the chromosomes, DNA, or proteins. The laboratory sends written test results to a person's physician or genetic counselor, or directly to the patient if desired. The heel of a newborn is poked.. In contrast to other forms of genetic testing, a parent is usually only informed of the results if they are positive. If the test findings are positive, more testing will be needed to determine whether the newborn has a genetic problem. Before doing a genetic test, it is vital to understand the testing technique, the benefits and drawbacks of the test, and any potential consequences. The process of telling a person about the test and obtaining their consent is referred to as informed consent. Direct-to-consumer genetic testing allows anybody to buy tests without first consu[15]

IV. THE USES OF GENETIC TESTING INCLUDE:

Newborn screening is performed immediately after delivery to detect genetic disorders that can be addressed early. Millions of newborns are tested in the United States each year. The US Health Services and Resource Administration recommends that states check for a set of 35 illnesses, however many do more.

Diagnostic examinations

Diagnostic testing is used to confirm or disprove a specific genetic or chromosomal condition. When a disease is suspected based on clinical signs and symptoms, genetic testing is usually used to confirm the diagnosis. Not all genes or genetic illnesses, however, are amenable to diagnostic testing, which can be performed before birth or at any time in a person's life. A person's decision on medical care and the management of the disorder can be influenced by the findings of a diagnostic test.

First, prenatal testing.

Prenatal testing is used to detect genetic or chromosomal abnormalities in a fetus before birth. This sort of testing is made accessible during pregnancy when there is a larger probability that the unborn child has a genetic or chromosomal problem. Prenatal testing may occasionally make a couple feel less unsure or aid them in making pregnancy-related decisions. It cannot identify every
possible genetic disease or congenital imperfection.

1.Predictive and presymptomatic testing:

a. Predictive and presymptomatic testing is performed to uncover gene variants linked to illnesses that manifest after birth, frequently later in life. When there are no signs of the illness at the time of testing, these tests might be valuable for people who have a family member who has a hereditary disorder. Predictive testing can reveal mutations that raise an individual's risk of acquiring genetically based diseases, such as some types of cancer.

b. Presymptomatic testing can indicate whether a person will experience the signs or symptoms of a genetic disorder, such as hereditary hemochromatosis (iron overload). Predictive and presymptomatic testing findings can help enhance healthcare decisions and reveal a person's predisposition to acquire a disease.

2. Forensic examination

DNA sequences are used in forensic testing to identify a person for legal purposes. Contrary to the procedures previously mentioned, forensic testing is not utilized to find gene variants linked to disease. With the help of such tests, criminal suspects can be ruled out or implicated as well as establish biological links (such as paternity) between individuals.15

Some medications function by attaching to certain molecules, known as receptor sites, on the body's cells. Some persons may produce receptors that do not interact properly with the medicine due to variations in the genes that code for the receptors. Additionally, the production of receptors may be influenced by genetic factors, resulting in some individuals producing more receptors than others. Cancer treatments are a few examples of targeted therapies. Cancer is a hereditary condition in which abnormalities in the DNA cause cells to proliferate and divide out of control, resulting in tumors.[16]

Pharmacogenomic testing results may be used by medical professionals to help with medication and/or dosage recommendations.[17]

Somatic and germline mutations can both be found through genetic testing. Gene mutations in tumors that are targets for anticancer medications can be found by somatic tissue testing. Mutations that enable prevention, early detection, or treatment can be found through genetic testing. A patient's risk profile might also be more clearly defined by a patient's ancestry. For instance, preventative treatment can considerably minimize or prevent the beginning of disease. Certain genetic biomarkers can help identify a person's vulnerability to ovarian or breast cancer.[18,19]

Pharmacogenomic testing allows for the detection of genomic factors linked to differences in drug response before treatment, ensuring that the benefit of a medication is maximized without the unintended consequences of ADRs[20]

V. PRESCRIPTION OF MEDICINE BASED ON PHARMACOGENOMICS CONCEPT:

better drug administration With the introduction of pharmacogenetics into patient care, the practice of trial-and-error medication prescribing may be removed. Clinicians will use genetic information to ensure that the correct treatment is given to the right patient at the right dose while minimizing adverse effects. This customized medicine technique will benefit patients suffering from a variety of disorders, including schizophrenia and depression, by hastening symptom improvement or recovery.21

For example, clopidogrel, an antiplatelet medication, could be given to two patients with comparable clinical presentations at the same dose, one of whom would have adequate therapeutic protection against cardiovascular events while the other would suffer a myocardial infarction due to insufficient therapeutic protection..22

A novel medical concept known as customized (precision) medicine for infectious illnesses employs molecular biology technology to provide faster, more accurate, and comprehensive diagnostic microbiology testing, allowing for more efficient therapy intervention.. 23

Comparative genomics has been utilized to find virulence factors, antimicrobial medicine targets, vaccine targets, and novel diagnostic markers by using the strong capabilities of bioinformatics and microarray technologies. 24

Knowledge of genetic susceptibility to infection has the potential to be extremely valuable; for example, resistance to HIV infection may be traced in certain cases to a mutation in a receptor protein (CCR5) that the virus uses to enter immune cells.

Though there are examples of how pharmacogenomics may alter pharmaceutical prescription, adverse event prediction, and medication dosage, pharmacogenomics' genuine use is still in its early stages. The day when all clinicians routinely utilize genetics to compute medication dose approaches as pharmacogenomics knowledge progresses and the infrastructure for its application matures.

Among the remaining obstacles include overcoming legislative barriers, finding systems for frequently updating existing discoveries, training clinicians, and integrating genetics into medicine. These concerns, however, have been rectified, and pharmacogenomics will very certainly be one of the first significant clinical uses of personalized genetic medicine. [25]

VI. WHAT ROLE DO GENES PLAY IN HOW MEDICINES WORK?

Our genes impact how our bodies react to drugs in the same way that they influence the color of our hair and eyes. Genes are DNA instructions that are utilized to build protein molecules. The same gene may occur in several forms in different people. The DNA sequence differs somewhat across variants. These variants are available in both common and unusual forms. Furthermore, some have an effect on health, such as gene variants linked to certain illnesses. The majority of genes are present in two copies each individual. Some people have hundreds or even thousands of copies of the CYP2D6 gene. Those with additional copies overproduce the CYP2D6 enzyme, which swiftly breaks down the medicine. Because of how quickly and fully their systems convert codeine to morphine, a standard dose

may be too much for certain people. Some CYP2D6 genotypes, on the other hand, generate an inefficient enzyme. These mutations result in slow or nonexistent codeine metabolism, resulting in little or no pain alleviation. Doctors may advise them to try a new drug. Certain proteins are known to impact the way drugs work. Pharmacogenomics investigates changes in the genes that code for these proteins. These proteins include liver enzymes, which chemically change drugs. Due to chemical changes, drugs can occasionally become more or less active in the body. Even little changes in the genes encoding these liver enzymes can have a big influence on a medicine's safety or efficiency.

It turns the painkiller codeine, for example, into its active form, morphine. The CYP2D6 gene has more than 160 variants. Many are distinguished by a single change in their DNA sequence. Others have seen more drastic alterations. The majority of these variations have no effect on how people react to the medicine. [26]

VII..APPLICATION OF PHARMACOGENOMICS FOR DEVELOPMENT OF MEDICINE:

Drug target selection criteria and pharmacogenomics: The first stage in the drug development process is to identify a potential target for the medication to act on. Any protein generated in a sick condition, any receptor, any transporter, any enzyme in a critical pathway, and any protein involved in signal transduction can all be targets. Pharmacogenomics can help in selecting the proper target for drug development, which is an important step. 27 2] Clinical Trials with Pharmacogenomics: The preclinical phase consists of a series of tests, the majority of which involve animals, to gather sufficient evidence of the therapeutic impact and safety, followed by clinical trials in healthy and unhealthy human volunteers to determine the medication's efficacy and safety..[28]

3] Pharmacogenomics for Predicting Drug Safety and Efficacy:

Variable Efficacy is a significant problem for medication development in addition to its direct clinical effects on individuals and healthcare systems. The most frequent justification for stopping drug development is failure to demonstrate efficacy in phase II studies. 29

4] Pharmacogenomics' Promise in Drug Discovery and Development: Pharmacogenomics offers the ability to solve two major issues in healthcare: the declining productivity of the drug discovery process and an unacceptable number of patients who do not benefit from or experience unfavorable side effects from medicines. 30

Pharmacogenomics can provide not just insights into possible phase II safety warnings, but also data to assist researchers and developers in making judgments. This application of pharmacogenomics data will be critical in aiding the rational creation of novel drugs. [31]

VIII. IMPORTANCE AND NEEDS OF PHARMACOGENOMIC

We can use a person's genetic composition to predict how quickly the body metabolizes medications and how well the body processes them. This will improve the therapy's efficacy and reduce the likelihood of an overdose. Similarly, knowing ahead of time how vulnerable a disease is would allow for thorough monitoring and the introduction of medicines at the optimal moment to optimize their therapeutic benefits.

Pharmaceutical firms will make drug development easier and allow drug makers to create medicines that are better tailored to certain conditions. This accuracy will not only improve treatment outcomes but will also protect surrounding healthy cells.

Pharmacogenomics is a promising tool in the pharmaceutical industry that should be exploited to its full potential.

It constitutes a quantum leap forward in medical history. Its primary goals include customized therapy, improved effectiveness and reduced adverse drug responses, genotype-clinical genotype correlation, discovery of novel targets for new medications, and pharmacogenetic profiling of patients to predict disease risk and drug response.

IX. CONCLUSION:

Pharmacogenomics is an important science used in in pharmaceutical industry to achieve maximum benefit to the patients. The main aims of pharmacogenomics is to improvement in efficacy and reduction in adverse drug reactions. pharmacogenetic profiling of patients to predict disease susceptibility and drug response. In the preceding, most of the drugs were designed to work on the population level but by the using the concept of pharmacogenomic drug being targeted for the individual patient to overcome particular disease. pharmacogenomics helps to refine the focus of treatment and makes drugs more effective and less toxic. 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

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