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Pharmacogenomics: An Update Review

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Abstract:- Pharmacogenomics studies how genetics affects how drugs affect the human body. The terms genomics and pharmacology are the sources of the field's name, which represents the intersection of genetics and medicine. The discovery of the laws of heredity in 1866 marked the beginning of the area of pharmacogenetics (PGx). The FDA has established PGx testing recommendations, so whenever these 250+ drugs are being reviewed, testing should be considered. Physicians in the fields of pain management, mental health, and cardiovascular health are among those who provide PGx recommendations. Antidepressant medications offer several therapeutic options that are similar, which makes them a prime candidate for the use of PGx. It makes sense that pharmaceutical companies are hesitant to use pharmacogenomics in clinical investigations given its relative youth. Clinical trials and pharmacogenomic testing together have many advantages. Finding populations with risk factors unrelated to the medication itself may also be facilitated by pharmacogenetics. Oral anticoagulants and chemotherapy treatment regimens are now recommended based on a patient's pharmacogenetic condition. When it comes to patient dosing, pharmacogenetic techniques are gradually replacing the traditional method of depending solely on trial and error. The present therapeutic application of pharmacogenetics can also be applied to drug research and development.

Keywords:- *Pharmacogenetics, Single Nucleotide Polymorphisms, Adverse Drug Events, Pharmaceutical.*

I. INTRODUCTION

The study of pharmaceutical effects on the human body as a function of genetics is known as pharmacogenomics. The terms genomics and pharmacology are the sources of the field's name, which represents the intersection of genetics and medicine. The promising field of pharmacogenomics holds the promise of tailoring pharmaceuticals in the future based on the distinct genetic makeup of individual patients. The way a person responds to medication can be influenced by a variety of factors, such as their diet, lifestyle, age, environment, and overall health. Personalized medication development, on the other hand, is thought to be made safer and more effective with knowledge of an individual's genetic makeup. A person's response to medication, both positive and negative, is influenced by several different genes. The lack of knowledge about the whole set of genes linked to drug response has hampered the development of genetic tests that can predict an individual's response to a particular medication. All of that changed when researchers discovered that individual genes differ slightly in the number of nucleotides in DNA.[1] As a result, genetic testing may now be used to forecast an individual's response to a treatment. Annotated gene, protein, and SNP databases serve as a bridge between pharmacogenomics and other traditional pharmaceutical sciences and biochemistry. In humans, single nucleotide polymorphisms, or SNPs, are the most common genetic variations. The human population has around 11 million single nucleotide polymorphisms (SNPs), or one SNP for every 1,300 base pairs on average. Various variables can be responsible for variations in pharmacological response. A patient's illness may not be properly treated by a medication regimen due to a variety of reasons. Medication interactions, disease-related changes in drug concentrations or responsiveness, patients not adhering to treatment plans, and errors committed by healthcare systems, including administering drugs or doses incorrectly, are a few of these. When racial or ethnic origin is associated with treatment non-responsiveness or adverse drug reactions, disparities in clinical outcomes may be made worse. The pharmacogenetic status of a patient is currently utilized to recommend oral anticoagulants and chemotherapy regimens for cancer patients to avoid adverse effects and treatment failures. When it comes to patient dosing, pharmacogenetic techniques are gradually replacing the traditional method of depending solely on trial and error. Pharmacogenetics is a tool that is now employed in therapeutics and can be applied to drug research and development.[2, 3]

II. EVALUATION OF PHARMACOGENOMICS

Pythagoras, around 510 BC, established the earliest documented link between pharmacogenetics and the finding that fava beans killed some people while sparing many others. Subsequent research revealed that a person's genetic composition, particularly a G6PD deficiency, affects this. With the development of the principles of heredity in 1866, the field of pharmacogenetics was launched.[4] Additional family studies conducted in the 1980s and 1960s confirmed patterns of inheritance for numerous medication effects, and molecular investigations revealed the heritable causes of several features. CYP2D6 became the first polymorphic human drug-metabolizing gene 13 when it was cloned and studied in 1987. In the 1990s, several genes, most notably TPMT (thiopurine methyltransferase)[5,6], showed promise for the therapeutic application of pharmacogenomics. Despite the slow adoption of this discovery in clinical practice at the

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time, it was found that the antileukemic and immunosuppressive thiopurine medications azathioprine and mercaptopurine caused hematopoietic toxicity in those with a hereditary impairment in this enzyme. Throughout the 20th century, notable advancements in the field included the detection of glucose-6-phosphate deficiency and other genetic metabolic disorders that may influence an individual's response to medication. When discussing how a person's genes determine how they respond to medications, the term "pharmacogenetics" was first used in 1957. The Human Genome Project was a massive worldwide endeavor that began in 2000 and ended in 2003 to understand how the human genome functions in physiological processes, with a particular emphasis on medication responses. The goal of several ongoing projects is to make it easier to convert genetic discoveries into diagnoses. Just two examples are the US National Institutes of Health (NIH) Pharmacogenomics Research Network and the Genomics England 100,000 Genomes Project. Over time, this research may aid physicians in more accurately prescribing and testing medications for each patient. Somatically acquired genetic variants in cancer and the identification and clarification of inherited variables influencing medicine response are important pharmacogenomic components of these and other endeavors.[7, 8]

III. WHEN TO CONSIDER PHARMACOGENOMIC TESTING

The FDA has established PGx testing recommendations, so whenever these 250+ drugs are being reviewed, testing should be considered. Individual PGx testing may also be considered in the following situations: taking four or more medications; being over 65; having two chronic medical conditions (diabetes, heart disease, or obesity/hypertension); having a personal or family genetics interest; experiencing an unexpected drug response; or wanting to actively manage one's health. [8] Several medical conditions can increase the risk of adverse drug events (ADE). These include myocardial infarction surgery, peptic ulcer, thyroid disease, osteoporosis, GERD, arthritis, asthma, COPD, cancer, diabetes, high blood pressure, high cholesterol, impaired liver function, mental health conditions, migraines, pregnancy, an enlarged prostate, and organ transplants. Adverse drug events (ADEs), poor response to alternative pharmacotherapy, cancer therapy, and the management of numerous concomitant conditions are the scenarios when testing is most likely to be covered.[9] However, insurance companies' coverage for PGx varies by plan and provider. PGx testing is more clinically beneficial when the medication's therapeutic window is narrow, the risk of adverse drug events (ADEs) is high, or the consequences of treatment failure are severe. Certain medications such as tricyclic antidepressants, neuroleptics, and cancer chemotherapeutics have restricted therapeutic windows and may cause severe side effects when concentrations exceed certain thresholds; warfarin is one such medication. The major goal of PGx testing is to find the optimum dose as quickly as feasible with the least amount of side effects possible.[10]

IV. IN WHICH PATIENTS SHOULD A PROVIDER CONSIDER PGx TESTING?

Physicians in the fields of pain management, mental health, and cardiovascular health are among those who provide PGx recommendations. Antidepressant medications offer several therapeutic options that are similar, which makes them a prime candidate for the use of PGx. The American Psychiatric Association's treatment guidelines for major depressive disorder (MDD) leave it up to the patient and provider to decide which of twelve possible medications is the best course of action.[11] When a patient's first treatment does not yield the desired results, the next step is frequently to suggest a different "first-line" treatment. PGx clinical guidelines can help direct the use of SSRIs and tricyclic antidepressants (TCAs) about CYP2D6 and CYP2C19 activity. According to this research, patients who received antidepressant prescriptions guided by PGx experienced fewer side effects and greater evaluations of depression. As such, PGx testing could be helpful for individuals considering initiating a new antidepressant medication. [12] When considering the time, PGx becomes much more seductive. It could take six weeks or longer to observe the full therapeutic benefit of SSRIs. Before realizing that one medication isn't working, the patient and the doctor may need to manage dose adjustments, appointments, and new prescriptions for several months. PGx testing may enable prompt determination of whether a lack of reaction signifies an insufficient trial or a pharmacological issue.[13] The usefulness of PGx testing depends on the potential severity of the response. Abacavir-based therapy for human immunodeficiency virus involves a risk of significant cutaneous side effects. Another well-researched area is the use of PGx to calculate the appropriate dose of the anticoagulant warfarin. The way that warfarin is administered may depend on several factors, including genetic variations, coexisting medical conditions, vitamin K intake in the diet, and use of other medications.[11,14]

V. ROLE OF GENOMICS IN THE DRUG DEVELOPMENT PROCESS

There are very few drug candidates that progress through clinical trials and are ultimately approved by regulators. [15] A large body of evidence suggests that drugs whose targets are validated by human genetic research have a higher chance of being commercially successful than those that do not. As a result, the significance of obtaining this data during the drug development process is increasing. Techniques such as GWAS and EHR-based phenome scanning—which involves searching for associations between specific changes in potential medication target genes and symptoms—are also being studied. The identification of rare sequence changes that appear to be linked to important human traits has also aided in the development of new medications. Initially, gain-of-function mutations in PCSK9 were associated with a notable elevation in LDL cholesterol and familial hypercholesterolemia [16]. This is undoubtedly the most well-known case. Subsequent studies from the Atherosclerosis Risk in Communities cohort and the Dallas Heart Study revealed that rare truncation (i.e., loss-of-

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function) variants, more prevalent in African Americans, were associated with markedly lower levels of LDL cholesterol and a dramatically lower lifetime risk of coronary artery disease [17]. These studies also prompted the development of PCSK9 inhibitors as a treatment for high LDL cholesterol. The original finding was made feasible by looking at an African-American cohort, and although the drugs have indications across ancestries, the indications are not limited to familial hypercholesterolemia. Several drug targets, such as APOC3 for hypertriglyceridemia, NPC1L1 for cholesterol transport, SLC30A8 for obesity-related diabetes prevention, ANGPTL4 for hyperlipidemia, and HSD17B13 for decreased risk of chronic liver injury, have been implicated or validated through the identification of rare sequence variants associated with unusual phenotypes. Additionally, human genetics plays a major factor in the creation of novel medications for uncommon Mendelian disorders. One minor mechanism of cystic fibrosis-related CFTR protein failure is altered conductance of typically surface-trafficking channels. Individuals with specific germline mutations who have either been studied in clinical trials or demonstrated improvement in function in vitro due to the drug's impacts on the drug's potential to boost functional status can currently purchase the conductance defect corrector, ivacaftor. Lumacaftor is marketed in conjunction with ivacaftor to treat cystic fibrosis, a condition marked by the incapacity of channels to reach the cell surface. If an initial study demonstrates that lumacaftor may correct cardiac potassium channel mistrafficking in a particular type of long QT syndrome, it may be used more widely, similar to other medications that correct protein mistrafficking in cells[18,19].

VI. PHARMACOGENOMICS AND CLINICAL TRIALS

It makes sense that pharmaceutical companies are hesitant to use pharmacogenomics in clinical investigations given its relative youth. Pharmacogenomic testing and clinical trials can be combined to yield several benefits. [20] The development of new medications is largely concerned with two factors: their safety and efficacy. Before the discovery of pharmacogenetic approaches, both of these characteristics had incredibly poor prediction values. Significant financial loss was incurred as a result of the medicinal ingredient's attrition during clinical trials. The landscape has changed recently, with the availability of very efficacious pharmacogenetic techniques that can significantly reduce the attrition rate. As a result, less money is wasted on the development of new medications. By utilizing in vitro methods to ascertain whether polymorphic enzymes metabolize the drug, a preclinical study can decide whether or not to move further. This information can help identify appropriate subjects with normal metabolizing enzymes and prevent adverse events in phase I clinical studies.[21] Crucially, understanding the drug's metabolic pathway is essential for applying pharmacogenetic principles as inclusion or exclusion criteria. Patients cannot be selected for exploratory trials using pharmacogenetic principles because there is insufficient information about the drug's metabolism. Nevertheless, pharmacogenetic information gathered early in a clinical investigation can be beneficial afterward.[22]

VII. PREDICTION OF EFFICACY OF DRUG

Unlike the traditional approach, which involves conducting preclinical and clinical research to establish efficacy—the decreased likelihood that a drug's ineffectiveness will result in study failure in both preclinical and clinical settings—medications developed with pharmacogenomic assistance already have an established effectiveness status.[23] Another application of pharmacogenomics is to determine who could benefit the most from taking a medication. A frequent example is the relationship that exists between changes in apolipoprotein E (APOE), cholesteryl ester transfer protein (CETP), stromelysin-1, and β-fibrinogen and the onset of atherosclerosis, cardiovascular events, and death. The findings demonstrated that those with these polymorphisms benefited more from HMG-CoA inhibitors than those without them. [24]

- *Pharmacogenetic in Patient Care*

The most popular pharmacogenetic test in patient care is the identification of polymorphisms in the genes that code for drug-metabolizing enzymes because it facilitates dose selection or modification. Finding populations with risk factors unrelated to the medication itself may potentially be a benefit of pharmacogenetics [25].

VIII. CONCLUSION

In pharmacogenomics, a few common gene variants that have significant impacts have drawn the most interest. The fundamental effects of pharmacogenomic variants vary, ranging from heterozygotes for reduction-of-function alleles to homozygotes for absolute loss-of-function alleles in genes essential for the disposition of particular drugs. Large-scale clinical trials, which usually focus on a single medication, have proven challenging to organize and carry out due to this broad spectrum of effects. Research on genomes has created new opportunities to study variations in pharmaceutical responses.

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