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AN OVERVIEW ON PHARMACOGENOMICS

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ABSTRACT

Pharmacogenomics examines the effects of medications on the human body as a function of heredity. This field is the meeting point of genetics and medicines; the name derives from the phrases genomics and pharmacology. The field of pharmacogenetics (PGx) was launched in 1866 with the establishment of the principles of heredity. Testing should be taken into account whenever these 250+ medications are being examined since the FDA has released PGx testing recommendations. Mental health, cardiovascular health, and pain management are just a few of the medical specialties that offer PGx recommendations. There are several comparable therapeutic choices for antidepressant medicines, making them an ideal candidate for the usage of PGx. Since pharmacogenomics is still in its infancy, pharmaceutical companies are understandably wary about using it in clinical studies. Numerous benefits can be achieved by combining pharmacogenomic testing with clinical trials. Pharmacogenetics may also be useful for identifying populations with risk factors that are unrelated to the medicine itself. A patient's pharmacogenetic status is now used to advise treatment regimens for cancer chemotherapy and oral anticoagulants. Pharmacogenetic approaches are progressively supplanting the age-old practice of relying on trial and error when dosing a patient. Drug research and development can also use pharmacogenetics, which is currently used in therapies.

KEYWORDS: Pharmacogenetics, Single nucleotide polymorphisms, Adverse drug events, Pharmaceutical.

INTRODUCTION

The pharmacogenomics field examines medications' effects on the human body as a function of heredity. This field is the meeting point of genetics and medicines; the name derives from the phrases genomics and pharmacology. The exciting prospect of pharmacogenomics is the possibility that, in the future, medications may be personalized according to each person's unique genetic composition. Many factors can affect how a person reacts to medication, including their environment, food, age, lifestyle, and health status. However, knowing someone's genetic composition is believed to hold the secret to developing safer, more effective personalized pharmaceuticals. Many distinct genes impact a person's medication response, which encompasses both good and negative responses. The development of genetic tests capable of predicting an individual's reaction to a certain medicine has been hindered by a lack of knowledge on the entire set of genes implicated in drug response. That all changed when scientists found that people's genes exhibit slight differences in the amount of nucleotides in their DNA.[1] Now, genetic testing may be used to predict how a person would react to a treatment. Biochemistry and other conventional pharmaceutical disciplines are brought together in pharmacogenomics by way of annotated gene, protein, and SNP databases. Single nucleotide polymorphisms (SNPs) are the most prevalent genetic differences in humans. On average, there is one single nucleotide polymorphism (SNP) for every 1,300 base pairs in the human population, which amounts to around 11 million SNPs.[2] Variability in pharmacological response can be attributed to many factors. Many factors contribute to the failure of a drug regimen to treat a patient's condition effectively. These include medication interactions, changes in drug concentrations or responsiveness caused by the disease, patients' lack of compliance with treatment plans, and mistakes made by healthcare systems, such as incorrect drug or dose delivery. Disparities in clinical outcomes may be exacerbated when there is a correlation between racial or ethnic background and treatment non-responsiveness or adverse drug reactions. To prevent side effects and treatment failures, a patient's pharmacogenetic status is now used to advise treatment regimens for cancer chemotherapy and oral anticoagulants. Pharmacogenetic approaches are progressively supplanting the age-old practice of relying on trial and error when dosing a patient. Drug research and development can also make use of pharmacogenetics, which is currently used in therapies.[3]

EVALUATION OF PHARMACOGENOMICS

In 510 BC, Pythagoras made the first known connection between pharmacogenetics and the observation that eating fava beans killed some people but did not affect many more. It was later shown that this is influenced by an individual's genetic makeup, most especially a G6PD deficit. The field of pharmacogenetics was launched in 1866 with the establishment of the principles of heredity.[4] Molecular investigations uncovered the heritable causes of several features after additional family studies from the 1980s and 1960s confirmed patterns of inheritance for numerous medication effects. Cloning and characterizing CYP2D6 in 1987 made it the first polymorphic human drug-metabolizing gene 13. Several genes, particularly TPMT (encoding thiopurine methyltransferase), demonstrated the possible therapeutic use of pharmacogenomics in the 1990s.[5,6] Although the discovery was slowly used in clinical practice at the time, it was discovered that individuals with a hereditary impairment in this enzyme had hematopoietic toxicity when administered the antileukemic and immunosuppressive thiopurine medicines azathioprine and mercaptopurine. The identification of glucose-6-phosphate deficiency and other hereditary metabolic abnormalities that may impact a person's reaction to medicine was one of several significant advances in the subject throughout the twentieth century.[7] It wasn't until 1957 that the word "pharmacogenetics" was used to describe how a person's genes dictate how they react to drugs. Initiated in 2000 and completed in 2003, the Human Genome Project was an enormous international effort to decipher the role of the human genome in physiological processes, with a focus on drug responses. There are several current initiatives aimed at facilitating the translation of genome findings into diagnoses. For example, the Genomics England 100,000 Genomes Project and the US National Institutes of Health (NIH) Pharmacogenomics Research Network are only two examples. In the long run, this research could help doctors choose and dose drugs more precisely for each patient. Important pharmacogenomic aspects of these and other endeavors include the identification and elucidation of hereditary factors influencing medication response and somatically acquired genetic variations in cancer.[8]

WHEN TO CONSIDER PHARMACOGENOMIC TESTING

Testing should be taken into account whenever these 250+ medications are being examined since the FDA has released PGx testing recommendations. It is also possible to think about doing individual PGx tests when: subject to four or more medications, adults over the age of 65, adults over the age of 40 with two chronic medical conditions (diabetes, coronary heart disease, or obesity/hypertension), a personal or family interest in genetics, a drug response

that is not expected, a desire to take an active role in managing one's health.[8] Several medical issues can raise the likelihood of adverse drug events (ADE). These include GERD, arthritis, asthma, COPD, cancer, diabetes, high blood pressure, high cholesterol, impaired liver function, mental health issues, migraines, pregnancy, an enlarged prostate, surgery following a myocardial infarction, peptic ulcer, thyroid disorder, osteoporosis, and organ transplants. Testing is more likely to be covered in the following situations: adverse drug events (ADEs), poor response to alternative pharmacotherapy, cancer therapy, and the management of many comorbid diseases.[9] However, insurance companies' coverage for PGx differs by plan and provider. If the therapeutic window of the medicine is small, the risk of adverse drug events (ADEs) is significant, or the repercussions of treatment failure are severe, then PGx testing is more clinically useful. Some neuroleptics, tricyclic antidepressants, and cancer chemotherapeutics have limited therapeutic windows and can induce severe side effects when concentrations surpass specific limitations; warfarin is a good example of this. Finding the right dose as soon as possible with as few side effects as possible is the main objective of PGx testing.[10]

IN WHICH PATIENTS SHOULD A PROVIDER CONSIDER PGx TESTING?

Mental health, cardiovascular health, and pain management are just a few of the medical specialties that offer PGx recommendations. There are several comparable therapeutic choices for antidepressant medicines, making them an ideal candidate for the usage of PGx. It is up to the patient and provider to determine which of twelve possible drugs is the best course of action for treating major depressive disorder (MDD), according to the American Psychiatric Association's treatment guidelines.[11] After a patient's first treatment fails to produce the desired results, the next step is often to suggest a different "first-line" treatment. When it comes to CYP2D6 and CYP2C19 activity, PGx clinical recommendations can help guide the usage of SSRIs and tricyclic antidepressants (TCAs). Patients who underwent PGx-guided antidepressant medication had fewer side effects and higher depression ratings, according to recent research. Consequently, PGx testing may be useful for patients thinking about starting a new antidepressant drug.[12] When taking the duration into account, PGx becomes even more alluring. The entire therapeutic response to SSRIs may not be seen for up to six weeks. It could take the patient and provider a few months of juggling dose changes, visits, and new prescriptions before they realize that one drug isn't working. Quickly determining if a lack of reaction indicates an inadequate trial or a pharmaceutical issue may be possible using PGx testing.[13] How serious the response might be determines whether PGx

testing is useful. Human immunodeficiency virus therapy with abacavir carries the risk of serious skin adverse effects. The use of PGx to determine the proper dose of the anticoagulant warfarin is another topic that has been extensively studied. Several variables might affect warfarin treatment, including genetic differences, other health disorders, dietary vitamin K consumption, and concurrent drugs.[11,14]

ROLE OF GENOMICS IN THE DRUG DEVELOPMENT PROCESS

The number of medication candidates that make it through clinical trials and are eventually approved by regulators is extremely low.[15] There is a lot of data to suggest that medications with targets confirmed by human genetic research are more likely to be commercially successful than those without. The importance of gathering this information in the medication development process is thus growing. Methods like EHR-based phenome scanning (i.e., looking for correlations between symptoms and certain variations in prospective drug target genes) and GWAS are also under investigation. New medication development has also been facilitated by the discovery of uncommon sequence variations that seem to be associated with significant human characteristics. At first, a remarkable increase in LDL cholesterol and familial hypercholesterolemia were linked to gain-of-function variations in PCSK9.[16] This is arguably the most notorious case. In the following years, research from the Dallas Heart Study and the Atherosclerosis Risk in Communities cohort demonstrated that rare truncation (i.e., loss-of-function) variants, which are more common in African Americans, were linked to significantly lower levels of LDL cholesterol and dramatically lower risk of coronary artery disease throughout life.[17] The development of PCSK9 inhibitors for the treatment of high LDL cholesterol was spurred to market by these studies. While the medications have indications across ancestries, the initial discovery was made possible by examining an African-American cohort, and the indications go beyond familial hypercholesterolemia itself. The identification of rare sequence variants associated with unusual phenotypes has been used to implicate or validate several drug targets.[18] These include APOC3 for hypertriglyceridemia, NPC1L1 for cholesterol transport, SLC30A8 for obesity-related diabetes prevention, ANGPTL4 for hyperlipidemia, and HSD17B13 for reduced risk of chronic liver injury. Human genetics is also playing a significant role in the development of new drugs for rare Mendelian diseases. One small mechanism of CFTR protein failure in cystic fibrosis is the changed conductance of usually surface-trafficking channels. The conductance defect corrector ivacaftor is currently available for sale to individuals who have certain germline variations that have either been evaluated in clinical trials or shown

improvement in function in vitro due to the drug's effects on the drug's ability to enhance functional status. Lumacaftor, in combination with ivacaftor, is marketed for the treatment of cystic fibrosis, a disorder characterized by the inability of channels to travel to the surface of cells. Lumacaftor, like other drugs that fix protein mistrafficking in cells, may find wider use if an early trial shows it can fix heart potassium channel mistrafficking in one kind of long QT syndrome.[18,19]

PHARMACOGENOMICS AND CLINICAL TRIALS

Since pharmacogenomics is still in its infancy, pharmaceutical companies are understandably wary about using it in clinical studies. Numerous benefits can be achieved by combining pharmacogenomic testing with clinical trials.[20] The development of new drugs is primarily concerned with two factors: their efficacy and their safety. Both of these parameters had extremely low predictions before the development of pharmacogenetic techniques. Attrition of the medicinal ingredient during clinical studies resulted in significant financial loss. The situation has altered recently, and there are now highly effective pharmacogenetic methods available that can drastically lower the attrition rate. This results in less money going down the drain on medication research and development. It is possible to determine whether or not to proceed with a preclinical study by using in vitro techniques to determine whether or not polymorphic enzymes metabolize the medication. In phase I clinical study, this data can aid in the selection of suitable individuals with normal metabolizing enzymes and the prevention of adverse events.[21] Importantly, knowing the drug's metabolic route is necessary for using pharmacogenetic principles as inclusion or exclusion criteria. Due to a lack of information on the drug's metabolism, pharmacogenetic principles cannot be used to choose patients for exploratory trials. Still, pharmacogenetic data collected early in a clinical study can pay dividends later on.[22]

PREDICTION OF EFFICACY OF DRUG

There is already an established effectiveness status for medications developed using pharmacogenomic assistance, as opposed to the traditional approach that involves doing preclinical and clinical research to establish efficacy—the reduced likelihood of a drug's ineffectiveness leading to study failure in both preclinical and clinical settings. Finding out which people might gain the most from taking a medicine is another use of pharmacogenomics.[23] The correlation between variations in apolipoprotein E (APOE), cholesteryl ester transfer protein (CETP), stromelysin-1, and β-fibrinogen with the

development of atherosclerosis, cardiovascular events, and mortality is a common example. The results showed that HMG-CoA inhibitors were more effective for individuals who have these polymorphisms compared to those who did not. [24]

PHARMACOGENETIC IN PATIENT CARE

The discovery of polymorphisms in genes that code for drug-metabolizing enzymes is the most often used pharmacogenetic test in patient care since it helps with dose selection or adjustment. Pharmacogenetics may also be useful for identifying populations with risk factors that are unrelated to the medicine itself.[25]

CONCLUSION

Some frequent gene variations with big effects have been the center of attention in pharmacogenomics. From heterozygotes with reduction-of-function alleles to homozygotes for total loss-of-function alleles in genes critical for the disposition of specific medications, the basic impact of pharmacogenomic variations varies. Because of this wide range of effects, large-scale clinical studies, which typically examine a single medicine, have proven difficult to plan and execute. Genome research has opened up new avenues for investigating pharmacological response variability.

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