Recent Advances in Pharmacogenomics and Clinical Pharmacology: A Systematic Review

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ABSTRACT

Pharmacogenetics is the study of how genetic variables impact individual differences in drug safety and effectiveness. Pharmacogenomics is a rapidly growing field of science that combines pharmacology, the study of drugs, with genomics, the study of genes, in order to create safe, effective doses of medication that are specifically adapted to each patient's genetic profile. Basically, for more than 50 years, the idea of pharmacogenetics remained unknown. Pharmacogenomics applications can be used to improve the discovery of new entities and their development in two different ways: first, by developing new entities to combat drug resistance or new drug targets, and second, by improving the pharmacokinetics and metabolism of existing entities to minimise drug level variations. The promoter or intronic region of genes often contains short sequences (about 6–20 bases) known as transcriptional regulatory domains that operate as transcription factor binding sites. After the human genome was sequenced, it was estimated that there were about 8000 potential therapeutic targets, of which 4990 could actually be acted upon- 2329 by antibodies and 794 by drug proteins. Through ligand binding experiments, 399 molecular targets from 130 protein families have been identified. As stated before, the cost of genotyping 1000 DNA samples would be $0.3 per genotype. However, when the cost is calculated for a single patient example, it totals more than 130 USD, which also includes the cost of the probe. Therefore, genotyping is economically advantageous if it is used for a wider scope, as would be the case if it is important for therapeutic purposes. In order to reveal links between diverse components that are interconnected and influence one another, advancement in personalized health care requires the fusion of a variety of different fields and technology. In conclusion, pharmacogenomics is the promising pharmacological aspect of drug design in the field of clinical pharmacology.

Keywords: pharmacogenomics, clinical pharmacology, genotype, transcription factor, drug design.

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INTRODUCTION

Pharmacogenetics is the study of how genetic variables impact individual differences in drug safety and effectiveness [1]. Pharmacogenomics is a rapidly growing field of science that combines pharmacology, the study of drugs, with genomics, the study of genes, in order to create safe, effective doses of medication that are specifically adapted to each patient's genetic

profile. Predicting the level of effectiveness of a medication for a certain patient is difficult due to individual variability in drug therapy response [2]. Various clinical variables, such as body size, age, sex, hepatic and renal function, and concurrent drug use, are known to alter therapeutic responsiveness. Along with these clinical aspects, pharmacological factors such as variations in metabolism, drug distribution, and drug-directed proteins also play a significant influence [2-4]. Variations in genes producing cytochrome P450 and other metabolising enzymes in plasma concentrations of various medications have recently shown the main drivers of interindividual variability [5].

Though, pharmacogenetics refers to monogenetic variations that affect medication response, and pharmacogenomics refers to the entire range of genes connected to the determination of drug efficacy and safety [6,7].

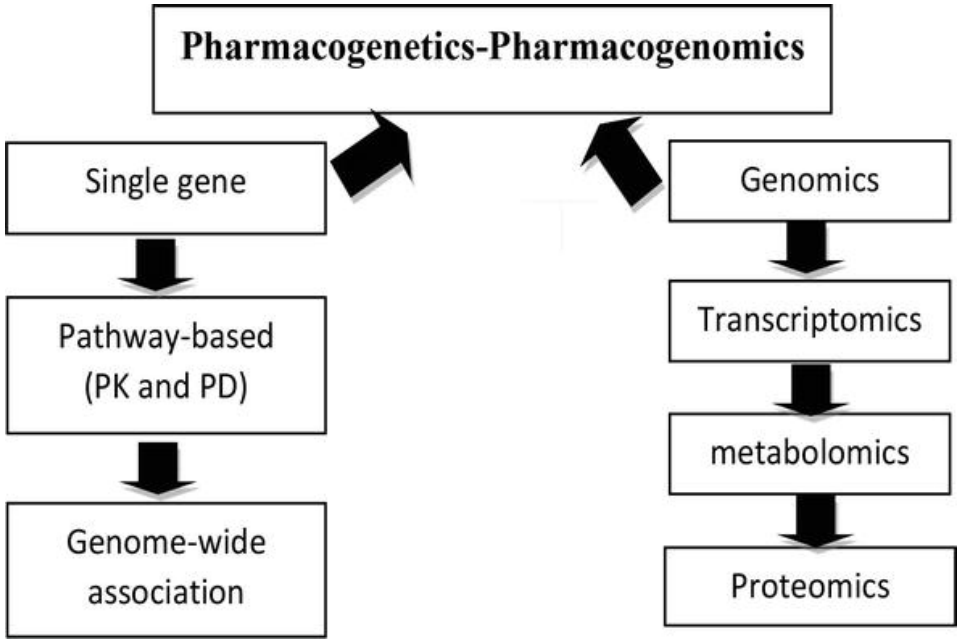

Fig 1. Depiction of pharmacogenetics and pharmacogenomics

Basically, for more than 50 years, the idea of pharmacogenetics remained unknown. Pharmacogenomics applications can be used to improve the discovery of new entities and their development in two different ways: first, by developing new entities to combat drug resistance or new drug targets, and second, by improving the pharmacokinetics and metabolism of existing entities to minimise drug level variations [8-10]. In actuality, individualised medication therapy or personalised drug therapy is a difficult endeavour. It requires multiple layers because, especially for complicated disorders, there may be a paucity of knowledge regarding drug action and critical disease pathogenesis genetic features. Large-scale clinical studies are also occasionally proving to be quite difficult for the researchers [11]. Pharmacogenomics' association with cancer would increase the number of anticancer medications with improved chemotherapeutic outcomes [12-15]. Examples of current clinical and pharmacological limitations where molecular-based mechanisms are implicated in a variety of medication responses were seen in patients diagnosed with related disorders are numerous [16-17]. Additionally, certain polymorphisms that exist at the genetic level in genes have been linked to altered drug reactions and a higher rate of ADRs in people [18].

Finally, pharmacogenomics-based drug development and its regulation will pave the way for innovative and focused medication development, advancing individual drug therapy that is secure, efficient, and affordable. Sir Archibald Garrod outlines the theoretical foundation of pharmacogenomics in his book "1939 Inborn Factors of Disease" [19].

Pharmacogenetics is the study of how a medicine affects a certain person's genetic makeup. This field of study combines pharmacology, functional research at the genetic level, and genomics. Together, these branches contribute to the creation of secure, potent pharmaceuticals with dosages that are likely customised for each person's genetic profile [20-24]. The principal clinically validated application of pharmacogenetics is mentioned in terms of the development of human genomic research. This fuels a revolution in medication therapy. As a result, illnesses like depression, viral infections, childhood leukaemia, and hypertension are treated or under control to improve the patient's quality of life. The majority of medications on the market now come in "one size fits all" packages, but they occasionally don't work the same way for everyone. Therefore, it is challenging to predict who will experience positive results and who will experience undesirable side effects. Additionally, scientists are learning about inherited gene variations and how they affect how the body responds to pharmaceuticals thanks to their substantial work on the Human Genome Project. Stevens-Johnson syndrome or epidermal toxic necrolysis, clopidogrel resistance, malignant hyperthermia, warfarin sensitivity and its resistance, and thiopurine S-methyltransferase deficiency are conditions in which an individual responds to particular medications [25].

Applications

1. There are currently several common diseases with well-established hereditary components that have significant rates of morbidity and mortality. According to their sibling analysis, the degree of hereditary influence on diseases like obesity and diabetes has been predicted [26, 27]. Similar to this, some uncommon gene mutations can offer a glimpse into the more intricate biological processes [28]. For instance, it is simple to illustrate how CETP (cholesteryl ester transfer protein) affects patients' HDL levels when the person has extremely high amounts of HDL in their blood [29-31]. Another instance involves a person with Janus kinase 3 (JAK 3) gene deactivating mutations who exhibits a severe combination of immune-deficient condition, since JAK3 inhibition was occasionally predicted to have an impact on human immunological suppression [32, 33]. Consequently, this prompted additional research using pharmacogenetics on medicines that block CETP and JAK3 [34]. Additionally, the development of pharmacogenomics has made it possible to identify the links between disease states and human genes, which has allowed for the appropriate choice of therapeutic targets.

2. In order to properly classify diseases, several academic institutions and pharmaceutical businesses are now focusing their research on the correlation between disease phenotypes and genetic variants [35, 36]. Although there is a significant potential to analyse the genetic variation that exists in patients due to the collection of medical phenotypes linked to DNA samples. By collecting the DNA of a specific patient, genetic variation can be investigated. This is illustrated in a study that found a direct link between phenotypic new lipase gene family and HDL levels in individuals who participated in lipid-lowering trials. According to published sources, the aforementioned research is founded on a strong theory that is related to the biological gene selection of candidates. Now that the selection of the genome is exclusively

based on phenotypic criteria, it is simple to cross-examine it [10, 37]. By utilising only a few numbers of haplotype-defining SNPs, these steps have now replaced over 300,000 SNPs across the genome. With the use of high-density oligonucleotide arrays connected to restriction enzyme-based genome reduction, Perlegen Sciences has created new genotyping technologies that are capable of genotyping large numbers of hundreds or thousands of markers. However, as these technologies develop, it is still unclear how many SNPs exactly define a certain haplotype. Recent research findings regarding the assessment of polymorphisms across specific gene areas suggest that in order to detect more than 80% of all haplotypes, a r2 of >0.8% is required. Scientists working on genes will thoroughly evaluate the degree of LD in a particular region or a selection of regions as a result of the HapMap project's progression with established LD patterns linkage. This will make it possible to investigate the topic of SNP selection further, regardless of study design [38, 39]. Understanding of complicated disorders like psychiatric or cardiovascular diseases will be more effective as the genome approach does not depend on the choice of candidate genes. The notion of a sizable genomic chunk area and its relationship with interest in phenotype, according to some researchers, will be shown by the new perspectives on LD coverage concerning insights of the human genome and SNP density [40]. 7283 SNPs connecting 17.1 mega bases (Mb) of DNA were genotyped for discovering links with HDL levels in order to evaluate the Perlegen Sciences chip-based array-based technology and to support the haplotype tagging approach for the detection of genetic relationships. Further, the greatest significant connection in the sample was revealed to be SNPs linked to 50 CETP haploblock genes. Companies like Perlegen and initiatives like the Hap Map project recently expressed their intent to introduce SNP markers into public domains as a basis for future scientific community-beneficial investigations [41].

3. The therapeutic outcomes and pharmacological usage are greatly expanded by pharmacogenetics. Patients who exhibit genetic predisposition to their adverse outcomes may be prescribed minimal doses of medication under rigorous monitoring. This would likely be beneficial for people who have the VKORC1 genotype linked to enhanced warfarin sensitivity to begin taking medicines with narrow therapeutic indices like warfarin gradually. Pharmacogenetics has made it possible to carry out experiments with fewer patients while also reducing the possibility of mistake for many disorders [42].

4. On the other hand, by matching the right drug to the right patient at the right dose, practitioners may be able to reduce the likelihood of side effects. As an illustration, the conventional method of managing hypertension is testing a variety of anti-hypertensive medications until the goal blood pressure is obtained with appropriate drug tolerability. Few initial medications/agents in this situation either failed to decrease blood pressure or had unpleasant side effects. This method of drug selection took a long time, which ultimately hurt the patients. Contrarily, pharmacogenetics, which is based on the DNA of the patients, provides the best response and drug tolerability. Pharmacogenetics may be able to create new treatments with fewer side effects because it is based on genetic regulators of cellular activity. For instance, the life-threatening nature of chronic myeloid leukaemia which is brought on by chromosome translocation and the enzymes it produces, has sped up FDA approval of the inhibitor of the translocation-created enzyme imatinib [43]. In the end, this important topic leads to the discovery of new genetic targets for disease management and improves the quality and lowers

the overall costs of healthcare by reducing the number of adverse reactions and treatment failures [44].

Effects of single nucleotide polymorphisms on metabolism

These sequence variants have the potential to alter the structure and function of the encoded proteins as well as the amount of gene expression. Protein function, however, might not be affected in any noticeable way. Patients getting conventional doses of medication may experience an unpleasant drug reaction or, in the latter two cases, fail to respond if they inherit these alleles. Such SNPs may be possibilities for alleles that alter medication responsiveness. SNPs in regulatory regions of genes may affect how genes are regulated in terms of expression [45]. The promoter or intronic region of genes often contains short sequences (about 6–20 bases) known as transcriptional regulatory domains that operate as transcription factor (TF) binding sites. The binding efficiency of transcription factors may be increased or decreased by SNPs that alter the binding location, leading to changes in the spatial pattern of gene expression or even the intensity of gene expression. Alternately, by introducing novel TF binding capabilities, SNPs in the promoter region may result in a gain-of-function. In the promoter of the gene for tumor necrosis factor, for instance, the minor "A" allele of an SNP creates a novel binding site for the OCT-1 TF, leading to enhanced transcriptional activity. OCT-1, on the other hand, does not bind to the same promoter that is overrepresented by the "G" allele [10]. The 5′ or 3′ untranslated region is finally another gene in the regulatory region that can be affected by SNPs [46].

These areas, which are on either end of the transcribed mRNA molecule, are subject to either translational suppression or modifications in mRNA stability during post-transcriptional regulation. Post-transcriptional control is carried out by the binding of regulatory factors, small non-coding RNA molecules with a length of 19-21 nucleotides, to sequence motifs in the untranslated region of the mRNA [47,48]. alterations in mRNA stability brought on by SNPs targeting these motifs in the 3′-untranslated region have been connected to alterations in regulatory protein [49] or microRNA binding properties [50]. Prototypes are terms used to characterize monogenic features in pharmacogenetics. They consist of variations in a single gene that codes for a protein that affects or affects how a drug is metabolized, leading to a range of individual reactions. Drugs must interact with specific targets that are limited to the cytoplasm, plasma, or cell layer in order to be effective. These effectors can be altered quantitatively to produce biological variability as well as genetically based illnesses. In both cases, administering a medication that is safe and effective for the general populace may have severe side effects in those who carry the illness gene and cause a subclinical alteration in a syndrome like the long QT syndrome, which is relatively uncommon but has clinical significance.

Table 1. Various genes used in different clinical conditions

Clinical Condition	Genes Associated	Clinical Usage	Reference
Atrial fibrillation	CYP2C9, VKORC1	Dose of Warfarin	[51]
Breast cancer	HER2	Use of Trastuzumab recommended	[51]

Epilepsy	HLA-B1502	Use of carbamazepine	[51]
Chronic myeloid leukemia	BCR and ABL	Imatinib is recommended	[52]
Cystic fibrosis	G551D, G551D	Ivacaftor is recommended	[53]

Drug development with pharmacogenomics

Finding a prospective target that a medication might target is the first stage in the drug discovery process. The target protein can be any protein produced by a disease, a receptor, a transporter, an enzyme in an essential pathway, or a protein involved in signal transduction. After the human genome was sequenced, it was estimated that there were about 8000 potential therapeutic targets, of which 4990 could actually be acted upon—2329 by antibodies and 794 by drug proteins [54]. Through ligand binding experiments, 399 molecular targets from 130 protein families have been identified [55]. Genetic variations are known to cause these targets to vary. Drugs having wide polymorphisms as targets can have a range of effects. As was already indicated, responder and non-responder phenotypes have been produced by polymorphisms in the 2-adrenoceptor gene, for example [57]. If a molecule like this is wanted as a medicine, it may lead to contradictory results in the subsequent preclinical and clinical tests. Other suitable targets can be chosen after such targets are removed as therapeutic molecules. So, utilizing pharmacogenetic and proteomic investigations, targets can be identified early on, and promising therapeutic molecules can be selected for further investment. Instead of a single gene mutation, variation in a disease's medication response is often caused by numerous genes. Since single gene alterations may be taken into account when numerous genes are actually implicated, the results of pharmacogenetic investigations have little therapeutic application. In such circumstances, pharmacogenomic investigations examining single nucleotide polymorphism (SNP) expression and heat maps across patients and controls would be appropriate instead of a pharmacogenetic research. With the aim of developing new drugs, this can identify the hereditary components linked to the disease condition and provide more up-to-date areas to characterize and evaluate [58].

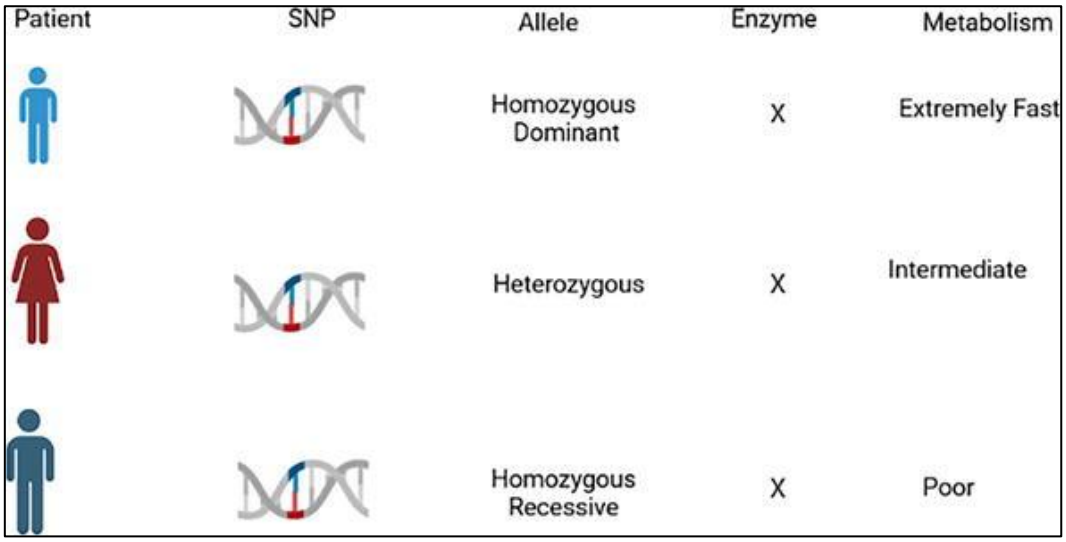

Fig 2. Consequences of polymorphisms on drug metabolism.

When pharmacogenetics is suggested in clinical practice with appropriately directed dosages, the targets that cause morbidity in poor metabolizers can really be avoided by applying pharmacogenetic gadgets and comprehending the causes of negative impacts. It is also important to understand that the group with low metabolizing ability due to genetic polymorphisms is a very tiny and uncommon subset. If an enzyme polymorphism is discovered in a broader population, the pharmaceutical company forgoes creating such a medicine. The cost of the patient's pharmacogenetic testing before starting treatment would be another concern. In many impoverished and underdeveloped countries, the cost of genotyping for single nucleotide polymorphisms may not be justifiable. However, as technology develops, this price can soon go down. As stated before, the cost of genotyping 1000 DNA samples would be $0.3 per genotype. However, when the cost is calculated for a single patient example, it totals more than 130 USD, which also includes the cost of the probe. Therefore, genotyping is economically advantageous if it is used for a wider scope, as would be the case if it is important for therapeutic purposes.

Clinical Pharmacology

The scientific field of clinical pharmacology examines every facet of the interaction between medications and people. Its scope includes the creation of novel drugs, their usage as medicinal agents, their positive and negative impacts on people and society, as well as their willful abuse. A wide range of professions, including doctors, pharmacists, nurses, and scientists in numerous fields, may find clinical pharmacology to be of major interest.

Clinical pharmacology has a long and recent history. Drug therapy has been utilized since the discovery of medications like quinine, reserpine, and artemisinin, which were initially employed as herbal remedies. Although William Withering's book on the use of foxglove in the treatment of heart failure [59] may very well be regarded as the earliest scholarly account of the field, it took another 200 years before the clinical pharmacology of digitalis was thoroughly investigated. Clinical pharmacology is a relatively new academic and scientific field that dates back to the middle of the 20th century. Since opinions vary between nations, it is challenging to determine who came up with the name originally. Drug evaluation was once a trial-and-error process, but several eminent pharmacologists working in the middle of the century brought pharmacology and clinical drug knowledge together and contributed to its transformation into a scientific field.

Harry Gold at Cornell is frequently credited for coining the term "clinical pharmacology" in the early 1940s in Anglo-Saxon literature [60]. However, Hans Horst Meyer and Rudolf Gottlied published a German textbook in 1914 with the working title "Pharmacology, Clinical and Experimental." Additionally, Paul Martini, a professor of medicine at Bonn who is regarded by some as the first clinical pharmacologist, released his monograph titled "Methodology of Therapeutic Investigation" in 1932 and is also mentioned in German literature. His efforts, according to Shelley and Baur, went unnoticed by the English-speaking world [61]. Clinical

trials have become an essential ingredient of new drug development and phases are shown as below-

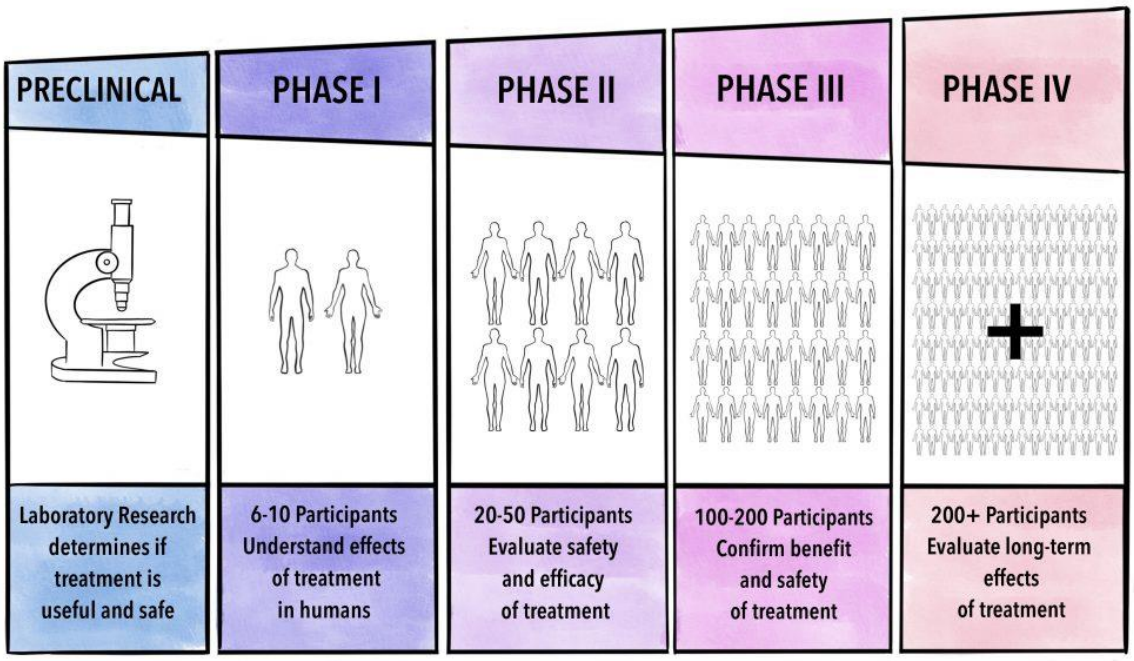

Fig 3. Phases involved in clinical trials

Without a question, the United States made the most active efforts to establish clinical pharmacology as an academic discipline [62]. The first edition of Goodman and Gilman's "The Pharmacological Basics of Therapeutics" and Walter Modell's successful attempt to start the first scholarly journal in the field, "Clinical Pharmacology and Therapeutics," both in 1960 at Cornell, are significant turning points [63].

The United States rose to prominence as the world's primary training ground for clinical pharmacologists in the early 1960s. James Shannon, the director of the National Institutes of Health, and his colleagues Bernard B. Brodie and Julius Axelrod established the fields of biochemical pharmacology as sciences and clinical pharmacology as a field of study. Potential clinical pharmacologists from all over the world had access to training at a number of top clinical pharmacology centres. Louis Lasagna, a student of Harry Beecher at John Hopkins Hospital, made attempts to enhance clinical medication evaluation; these efforts deserve special recognition. A superb and still relevant overview of the current state and potential future growth of clinical pharmacology was written by Lasagna in Science in 1966 [64-65].

In order to publish a report on the scope, administration, and education of clinical pharmacology, WHO assembled a Study Group in 1970 [66] under the direction of the late Sir Derrick Dunlop of the United Kingdom, which also included late academics Louis Lasagna of the United States, Franz Gross of Germany, and Leon Goldberg of the United States. The roles of clinical pharmacology in teaching, research, and healthcare were the subject of a handbook and a number of articles published in the European Journal of Clinical Pharmacology by WHO

Europe in 1991 [67]. The potential value of the discipline for the RUD in primary healthcare was highlighted for the first time.

CONCLUSION

Knowledge of customized medicine provides earlier disease identification by improved use of current biomarkers and the discovery of early genomic and epigenomic events in disease progression, including carcinogenesis. The major goal of this strategy is preventative medicine, which promotes proactive rather than reactive interventions. This method postpones or eliminates the need for more potent medications, which are typically more tolerable and have increased financial and personal satisfaction considerations. Government-funded healthcare systems are under more strain globally as a result of rising healthcare expenses, particularly for end-of-life care. By eliminating the drawbacks of alternative treatments, precision medicine may improve the effectiveness of currently used therapies. With the help of a patient's hereditary or genetic profile, a doctor can select a therapy that may not only ensure greater success and reduce unfavourable side effects, but may also be less practical and a "experimentation" method of treating the illness. Precision medicine is a rapidly expanding field of medical services. Healthcare expenditures are rising due to the "trial-and-error" non-precision medicine method, which is less successful and can lead to drug toxicity, serious side effects, reactive treatment, and misdiagnosis. The development of customized medicine will lead to a more cohesive treatment approach adapted to each person and their genome. With earlier intervention, more effective pharmaceutical innovation, and more targeted therapies, customized medication may produce superior results.

In order to reveal links between diverse components that are interconnected and influence one another, advancement in personalized health care requires the fusion of a variety of different fields and technology. In conclusion, pharmacogenomics is the promising pharmacological aspect of drug design in the field of clinical pharmacology.

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Nil.

CONFLICT OF INTEREST

'None' conflict of interest was declared by the authors.

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