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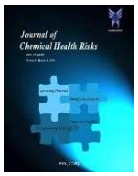

Revolutionizing Contemporary Medicine with Pharmacogenomics and Personalized Treatment - A Comprehensive Review

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ABSTRACT

Pharmacogenomics, commonly referred to by the term pharmacogenetics, is the scientific field that examines how someone's genetics affect their ability to respond to medications. It seeks to influence the creation of medications and therapeutic effectiveness. Pharmacogenomic study examines the entire genome in addition to the consequences of particular genes. A greater understanding of genetic variability offers the potential to reduce ADRs, and some of those that were once thought to be unavoidable may no longer be. To comprehend the variety in medication response, pharmacogenomic approaches can be applied, such as haplotype analysis, genome-wide scans, and target gene techniques. The pharmaceutical industry should make full use of the potential of pharmacogenomics Despite the fact that pharmacogenetic studies are already extensively employed for research purposes, they must start to be used in the development of new pharmaceuticals at extensive level. The main determinants of a new pharmaceutical compound's success—namely, tolerability & efficacy—have grown increasingly predictable alongside the growth of pharmacogenetic studies. Pharmacogenetic techniques are now employed globally, notably for determining the efficacy and safety of medications The ability to incorporate testing into clinical treatment has only been made possible by a relatively small portion of pharmacogenetic research. Haplotype analysis and genome-wide scan procedures were created as a result of the realisation that multiple genes needed to be investigated. However haplotype analysis and genome-wide scans won't be used in clinical practise for patient testing because of the present expense of analysis for patients. However, similar techniques may be used in the pharmaceutical industry's drug development process. Pharmacogenomic research will someday be included into the process of discovering new drugs, saving money, ensuring the safety of clinical trials, and lowering failure rates. As a result, numerous potential drugs which might have been avoided owing to their impact on study outliers can be kept if pharmacogenomic studies are used in the future.

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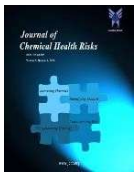

INTRODUCTION

Hereditary abnormalities in around 20 genes have been identified after decades of study; these variations affect about 80 medications and may be managed in the clinic. Additionally, certain somatically acquired genetic variants affect the patients' choice of "targeted" anticancer medications. Current initiatives that focus on the methods required to properly respond to pharmacogenomic variability in the clinic are laying the groundwork for precision medicine. In order to improve medicine usage, these initiatives are moving away from discovery and towards the implementation of an evidence-based strategy.[1] The outcomes of drug therapy are typically unexpected and might range from beneficial effects to ineffectiveness to serious negative effects. The field of pharmacogenetics examines how certain gene variants could cause such unpredictability. Genes that control drug transport, drug metabolism, disease susceptibility, or pharmacological targets may be responsible for these alterations. The genetic analysis for the genome of humans including documentation related differences among human genomes have made the fledgling field of pharmacogenomics viable, which investigates the idea, that genetic diversity underlies heterogeneity in pharmaceutical responses.[2] Individual drug responses differ from one individual to the next, and occasionally results are unexpected. DNA polymorphisms that alter the expression or activity of proteins that medications target can have a significant impact on individual variances in responses. However, future developments will depend on how effectively we can decipher the intricate multi-gene aspects that affect treatment response. Many of the genes examined in early research were connected to single-gene features that were extremely penetrant. The merging of genomics and medicine may lead to a new set of molecular diagnostic tools that may be utilised to tailor and enhance pharmacological therapy. Pharmacogenetics studies inherited differences in how individuals respond to drugs.[3] Among the most well-known instances are drug-metabolizing enzymes' mutations that affect 30% of all drugs. Due to thiopurine S-methyltransferase (TPMT) loss of function, patients who receive standard mercaptopurine doses with azathioprine incur substantial and potentially deadly haematological damage. Cytochrome P4502D6 (CYP2D6), which metabolises several antidepressants, has been linked to gene duplication as a cause of poor response to antidepressant medication. More and more genetic variants in pharmacological targets have been shown to influence how well a patient responds to treatment.[4] The effectiveness and toxicity of many drugs vary between individuals due to genetic variations in enzymes that metabolise drugs, carriers, sensors, and other pharmacological targets. Pharmacogenomic research is improving drug development by quickly identifying the hereditary causes of these variations in medication distribution & consequences. It also provides a more solid scientific foundation for tailoring pharmaceutical treatment based on the unique genetic make-up of each patient.[5]

PHARMACOGENOMICS

The potential use of the patient's DNA sequence is the pharmacogenomics' greatest hope. To improve drug therapy to increase effectiveness, only provide drugs to patients who are likely to respond, and prevent adverse drug reactions (ADRs).[6] Pharmacogenomic data has the potential to decrease the frequency of ADRs while simultaneously boosting the proportion of patients who respond to a treatment plan.[7] More stronger and selective drugs are predicted as a result of pharmacogenomics, and the FDA has taken seriously reported adverse drug responses and drug withdrawals. The number of "black box warnings" or "black label warnings," which are FDA-mandated advisories to likely adverse events, has drastically increased lately. More than 2 million major adverse drug reactions are reported to happen every year in the US, and they can lead to up to 137000 fatalities.[8] According to a personalised medical approach to a patient with an illness, the patient's genetic profile will enable the selection of a particular pharmacological therapy that leads to less severe adverse drug responses and an improvement in the identification of the disease's underlying cause.[9] For instance, advised novel dosing regimens for warfarin while examining the impact of genetic variations in the two enzymes that metabolise CYP2C9 and VKORC1. The FDA advisory panel suggested genotyping for all patients taking the medicine to guarantee that they receive the correct warfarin dosage the first time and to prevent adverse drug reactions.[10,11] The FDA has authorised the use of a molecular test called "Invader UGT1A1" that is part of the colorectal cancer medication irinotecan HCl for

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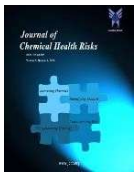

locating individuals who may be more likely to experience negative side effects from the treatment. Pharmacogenomics is a branch of science that investigates how a person's genetic make-up affects how they react to drugs. As its name implies, it combines knowledge of genomes with medicines. By connecting the regulation of genes or as single-molecule polymorphisms (SMP) in relation to a medication's effectiveness or toxicity, this strategy investigates the impact of genetic variation on patient treatment response. With the goal to achieve optimum efficiency with the least amount of side effects, pharmacogenomics strives to create practical techniques to improve pharmaceutical therapy with relation to the genotypes of patients. Such tactics herald the advent of "personalised medicine," in which drug formulations and dosages are adapted to each person's unique genetic makeup.[12]

ADVANTAGES OF PHARMACOGENOMICS

Pharmacogenomics has the possibility to provide individualised pharmacological therapy based on genetic differences in therapeutic effectiveness and adverse effects.[13]

- To anticipate a patient's response to medication, create individualised prescriptions, and reduce or completely get rid of side effects.
- To increase effectiveness and patient adherence.
- To enhance thoughtful medication development.
- To increase the precision with which suitable pharmacological doses are calculated.
- To detect and track certain illnesses.
- To create stronger, safer vaccinations.
- To enable advancements in pharmaceutical research and development (R&D) and the acceptance of novel medications.

Newly Powerful Substances

- Drug companies will get access to novel, potent chemicals thanks to maximum curative efficacy and minimal negative effects thanks to pharmacogenomics.
- More potent medications, better and safer medications were initially introduced.
- New Techniques for Determining the Appropriate Drug Dose.
- The techniques are decided by an individual's genetic makeup, which determines the speed at which the body metabolises the medication and the way long it takes.
- Understanding a patient's genetic composition can help with treatment, and methods like DNA analysis have given pharmacogenomics a new dimension. Pharmacogenomics can significantly contribute to patient care while minimising negative effects.[2]

NEED FOR PHARMACOGENOMICS

Pharmacogenetics study spans a wide range of topics. Understanding in enzymes like cytochrome P450, the impacts of gene polymorphism can be helpful for medication delivery, drug discovery & therapeutic drug usage. Utilising reasonably priced genotyping tools, doctors may treat patients. Although it is anticipated that this will soon change, genotyping is not yet a clinically acceptable practise. Pharmacogenomics and personalised therapy reveal higher efficacy and safety of treatment in accordance with FDA standards on pharmacogenomics, but they also contain ethical, social, and racial problems as crucial ones that need to be examined. The results of pharmacogenomics can be improved by making utilisation of innovative techniques for mining information & rapid screening.[10]

PHARMACOGENOMICS IN THE TREATMENT OF DIFFERENT DISEASES

Warfarin treatment

Thromboembolic disorders are treated with strong anticoagulants like warfarin.[14] It is given to people with atrial fibrillation and is given to individuals as a prophylactic strategy before undergoing major orthopaedic surgery. Adjusting the dosage, however, is a little challenging owing to this constrained therapeutic window. Whenever a larger dose is used, bleeding could happen, and patient responses might differ from person to person.[15] Giving the drug at the right dosage is therefore the largest issue for the doctors. SNPs are the sequences that change a gene's allele composition. Two variants that together make up the Mutation Cytochrome 2C9 and are known to be the cause of excessive anticoagulation are 432 C>T and 1075A>C, accordingly.[16] The process of regrowth from the decreased antioxidant vitamin K (KH2) cofactor, that is necessary for the production of clotting components, is

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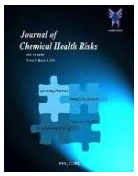

controlled by vitamin K epoxide dehydrogenase. Warfarin inhibits VKORC1 in an inefficient route, preventing the whole network from functioning. The major goal of CYP2C9 and VKORC1 screening is to assist the physician in prescribing a lesser amount of warfarin as that will have fewer side effects related to gastrointestinal bleeding & decrease the danger to the individuals being treated.[14,16]

Codeine

Possessing multiple versions on cytochrome P450 2D6 genes, which transforms codeine into morphine, the drug's active metabolite, enables nursing mothers to metabolise codeine more effectively than non-nursing adults. Breast-feeding mothers can thus have a lot of morphine and codeine in their milk. As a result, pharmacogenomics in relation to plasma morphine level might be used to monitor the administration of codeine to nursing mothers.[15]

Human Leukocyte Antigen

While taking antiepileptic drugs, it was shown that individuals having Stevens-Johnson syndrome, also known as (SJS) and toxic epidermal necrolysis of the skin (TEN) had the variant of human lymphocyte antigens (HLA) gene HLA-B*1502.

This gene is commonly found in South Asian people, which is consistent with the geographic variety of those people. Patients in SJS and TEN had high rates of death and also disability, and several of the survivors had long-term complications such impaired vision, renal failure etc. Because of this, it is essential to genotype HLA-B*1502 prior to administering a medication known as to dangerous Southeast Asians whose prevalence of the HLA-B*1502 gene is higher to prevent potentially deadly scenarios.[17–19]

HIV treatment

The identification of another among the worldwide biggest issues has become HIV right now. As a result, it is likely that the patient who was treated using traditional techniques would acquire medication resistance, making it impossible to stop the virus from spreading.[20] Therefore, more responsible medication usage and combination therapy are needed to completely eliminate the infection. The TRUGENE HIV-1 Genotype Kit is being offered for sale in order to diagnose HIV. [21]

Breast Cancer

Breast cancer remains among the most typical type of disease that affects women globally. Breast cancer affects 1/8 women at some time in their entire lives.[22] Numerous internal as well as external elements can lead to the emergence of several distinct cancer kinds.[23,24] Finding markers that might foretell a person's future or a tumor's response to a certain treatment has become an essential aspect of cancer research. In order to evaluate whether patients will benefit from effective therapy, only HER2/neu and the oestrogen receptor (ER) are used in conventional breast cancer screening.[25,26]

Carcinomas, or carcinogenic epithelial tumours, account for the majority of breast cancer cases. Sarcomas, which can develop form bones, flesh, muscle, or fibrous tissue, account for fewer than one percent of cases of breast cancer. Approximately seven percent of breast cancers were globular carcinomas, which grow in the lobes where milk is generated; while, roughly 75 percent of female diseases were duct cancers called carcinomas which occur in the tissues lining milk ducts. LCIS (lobular carcinoma in situ) and DCIS (ductal carcinoma in situ) are the terms used to describe cancers that are still confined within the duct or lobule, respectively. The terms "invasive or infiltrating ductal carcinoma" (IDC) or "lobular carcinoma" (ILC) are used to describe ductal or lobular carcinomas that invade neighbouring tissue. Around 95% of cases of breast cancer are estimated to be invasive.[27,28]

Diabetes

A metabolic condition characterised by hyperglycemia and other metabolic abnormalities brought on by a relative or absolute insulin insufficiency, among the least frequent illnesses in underdeveloped countries is diabetic hyperglycemia. More than 400 million people may be negatively impacted by it by 2030.[29,30]

Hepatocyte nuclear factors 4 (HNF4), a component of transcription that controls the transcription of genes, is encoded by the pancreatic beta cells. HNF4 has been connected to the regulation of glucose transport and metabolism besides to its primary function in regulating hepatic genes. Maturity-onset diabetic in the youth (MODY), a rare autosomal-dominate; insulin-

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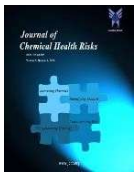

independent form of diabetic may result from mutations in this gene.[31,32]

Type 1 diabetes is a disease that is autoimmune. Whenever the immune system's protection to infections specifically targets a particular bodily part, an autoimmune illness develops. Insulin resistance, a condition that is additionally linked to considerably less insulin output, constitutes one among the greatest critical public health issues. This is a trait of type 2 diabetes. The key contributors to the increased prevalence of Type 2 diabetes include decreased physical activity, consuming unhealthy foods and eating more when one is genetically susceptible. People with type 2 diabetes are more prone to develop cardiovascular illnesses (CVD). The insulin receptor, or IR, is thought to contribute to the reduced responsiveness of tissues inside the body to insulin.People with type 2 diabetes may be administered a variety of diabetic drugs, including aglucosidase inhibitors, biguanides, meglitinides, sulfonylureas, and thiazolidinediones. When it comes to how oral anti-diabetic drugs perform and their adverse side effects, such as hypoglycemia, there is a lot of interindividual variance. The bulk of oral anti-diabetic drugs are metabolised by class 2C genetically polymorphism cytochrome P450 enzymes. Thiazolidinediones and repaglinide are biotransformed mostly by the enzyme CYP2C8, whereas sulfonylureas are predominantly CYP2C9 substrates.[27, 33–35]

Colorectal Cancer

The epidermal growth factor receptor, also known as EGFR is an important treatment option in cancers of the GI tract, notably cancer of the intestines. Stimulation of the EGFR stimulates a minimum of 5 inside of cells indicate flows including RAS/RAF/MEK (mitogen triggered ERK pathway triggering kinase)/ERK (extracellular signal-regulated kinase), PI3K (phosphatidylinositol 3-kinase)/PTEN (phosphatase along with tensin homolog)/AKT (v-akt murky lymphoma widely an oncogene homolog), STAT (signal sensor alongside activation for transcription), phospholipase as well as SRC/FAK (focal attachment kinase).[26,36] The malignancy of the colon genetics heavily depend on the proto-oncogene BRAF. BRAF controls the division and differentiation of cells via influencing the MAP kinase/ERK pathway. Aggressive melanomas, gastrointestinal & colorectal cancer carcinoma from developing, as well as other cancers, frequently exhibit the Val600-to-Glu (V600E) alteration that is brought on through the 1799T-A transversion within the BRAF genome.[37,38]

Cardio Vascular Diseases

Pulmonary embolism, cerebrovascular disease (CVA), peripheral arterial disease (PAD), rheumatic heart disease and congenital heart disease are among the illnesses classified as cardiovascular diseases (CVDs), which damage the heart and blood arteries. Associated with CVDs in a substantial way is essential hypertension. It appears that the study of pharmacogenetics offers some fresh perspective on the topic of varying treatments for cardiovascular illnesses.[39,40] For a variety of beta-blockers, which are among the most frequently given medicines in patients with cardiovascular problems, the possible effects of genetic polymorphisms in drug metabolising enzymes such CYP2D6 were assessed.[41,42] Metoprolol is primarily metabolised by the enzyme CYP2D6, and the pharmacokinetics of the medication clearly differ between CYP2D6 extensive and quick metabolizers. The pharmacodynamic response to the administration of metoprolol is also known to be impacted by CYP2D6 polymorphism. A potential option for pharmacogenetic data evaluation in therapy optimisation is the family of drugs known as sartans, which are used to treat hypertension or heart failure. The majority of sartans are metabolised by the genetically variable enzyme CYP2C9. Depending on the ethnic group, the genes that encode the CYP2C19, CYP2C9, CYP2D6, and CYP3A4/5 isoenzymes are highly polymorphic and show substantial allelic variation.[43–45]

Schizophrenia

Schizophrenia, the most severe mental illness, has a yearly cost of almost US$40 billion in the USA alone and is extremely painful for both sufferers and their families. Schizophrenia is a lethal illness: 10% of those who have it commit suicide, and the condition itself is associated with a nearly sevenfold increase in mortality when compared to the general population.[46,47] Despite significant advancements in the treatment of schizophrenia and countless insights addressing its pathophysiology and etiology, little is understood about these topics. But a number of schizophrenia-related

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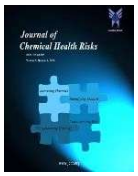

factors, including its incidence, age of beginning, symptom profile, and responsiveness to pharmaceutical therapy, provide evidence in favour of more research into the etiology and treatment of this illness. After the first neuroleptics were discovered, it took more than 10 years before the rare substance clozapine was available for clinical testing. Its clinical profile encouraged the creation of a new classification system for neuroleptics, with atypical (or novel) neuroleptics treating both the positive and negative symptoms of schizophrenia without EPS, and typical (or conventional) neuroleptics producing extrapyramidal side-effects (EPS) and antipsychotic effects. Pharmacogenomic research is important because of how differently schizophrenic patients respond clinically to antipsychotic medications in general and to clozapine in particular. Only a small percentage of patients receive typical antipsychotic medicine that has no therapeutic effects at all, and even fewer patients get a treatment that entirely removes the stigma attached to the condition. Clozapine has been shown to have improved therapeutic outcomes in patients (30–40%) who do not react well to traditional treatments.[48]

Alzheimer's Disease

The most frequent cause of dementia in elderly adults, AD affects 10% of those over 65 and 45% of those over 85 years of age. As a result of AD, which causes more than 100000 deaths each year, more than half of the nursing home residents in the US require that level of care. Unlike mental diseases, AD has a neuropathology that may be utilised to identify the disease, including extracellular amyloid plaques and intraneuronal neurofibrillary tangles. However, given that psychiatry treats and manages AD patients more frequently, the issue ought to be taken into account in this setting. A small but significant number of AD patients are known to have autosomal dominant transmission (familial AD), and at least three genes (those encoding amyloid precursor protein, presenilin 1 or presenilin 2) are associated to this early onset disease. Despite the fact that the origin of AD is unclear, familial AD is known to have autosomal dominant transmission. Additionally, research has unequivocally demonstrated that the E4 allele of the apolipoprotein gene confers a significant risk for late-onset, sporadic AD, which is the most common type of the disease[25]. All AD-related pharmacogenomic research conducted to far has primarily focused on this allele as a result (Table 1). Acetylcholinesterase inhibitors are the core of AD's limited pharmacotherapy, which aims to delay progression and ameliorate early cognitive loss, despite the disease's extensive and expanding molecular knowledge. Given the possibility that other genetic markers for the disease will likely become accessible in the future, more pharmacogenomic study may be anticipated.[46,49]

Table - 1: The pharmacogenomics of Alzimer Diseases

Candidate gene and polymorphism	Findings	Sample
APOE: E4 allele	E4 appears to predict poor response to therapy with acetylcholinesterase inhibitors: >80 of E4-negative patients showed marked improvement but 60% of E4 carriers worsened from baseline	N = 40 AD patients (22 E4 carriers, 18 non carriers)
APOE: E4 allele	Association between E4- negative genotype and improved response to tacrine	N= 460 AD patients (291 E4 carriers, 169 non carriers)
APOE: E4 allele	Associated between tacrine response and gender/genotype: E4 women showed worst treatment response, whereas E4 and E2-3 men showed no difference in treatment response	N= 528 AD patients

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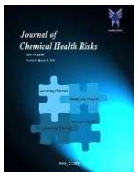

APOE: E4 allele	Association between xinomiline response and genotype: E4 patients showed no improvement after 6 months of treatment.	N=180 patients with mild to moderate AD
APOE: E4 allele	Association between E4 and response to S12024(an experimental medication for AD), a noncholinergic agent: E4 carriers showed better response	N=404 patients with probably AD (60% E4 carriers, 14% homozygotes)
APOE: E4 allele	No association between E4 allele and response to tacrine: no association between E4 allele, gender, and tacrine response	N= 76 AD patients (33 E4 carriers, 43 non carriers)
APOE: E4 allele	Data suggest that APOE genotype affects response of cortical electrical around to cholinergic therapy	N= 19(5 E4/4; 6 E4/3: B E3/3)
APOE: E4 allele	Association between absence of E4 allele and better response to tacrine	N= 232 patients, (105 placebo-treated, 127 Tcrine-treated)
APOE: E4 allele	Association between E4 homozygosity and poor response to xinomiline (M1- specific cholinergic against)	N= 41 (9 E3/3, 18 E4/3, 14 E4/4)

TECHNIQUES IN PHARMACOGENOMICS

Single nucleotide polymorphism (SNP)

SNPs, which are the consequence of single base-pair differences in chromosomal sequences brought on by point mutations, might be the reason why the human genome is genetically different from other genomes. A range of computer techniques and laboratories are used to find single nucleotide polymorphisms (SNPs) inside a genome. SNPs can be recognised using expressed sequence tags (ESTs), which are generated by single run sequencing of cDNAs obtained from multiple people. Non-coding SNPs can be divided into groups based on whether they are found in areas of the genome that control the activity of particular genes. Numerous complex disorders may develop as a result of quantitative differences in gene products rather than qualitative alterations. If an SNP affects the protein sequence that the altered gene produces, it can be categorised as a coding SNP.[49,50] Pharmacogenetic testing could be a useful resource for patients. This allows us to classify individuals and identify the specific pharmaceutical dose regimen that will have the greatest therapeutic effect. Thanks to important advancements like the availability of a large number of single nucleotide polymorphisms (SNPs), the Haplotype map (Hap Map), and the Roche microchip for microarray, we have come closer to producing genomic medicines. With this knowledge, we can now investigate the drug metabolising and drug-transporting enzymes that were identified as being in charge of the genetic alterations and establish whether the variance in the person is true.[20]

DNA-microarray technology

DNA chips and genome chips are other names for DNA microarrays. A group of small DNAs are attached to a strong base that is mainly constructed of silicon, glass, or plastic. The Southern-blot method, which relies on identifying certain sequences in addition to DNA fragments that have been eliminated by gel electrophoresis, is where the genome chip technology originated.[50,51] The Southern blot was the inaugural array produced using this method. The grid-based libraries were then stored in microtiter plates and afterwards immobilised with filter membranes after being screened using filter-based clone libraries. It was created by Pat Brown and associates and entails placing and immobilising molecules of interest on activated surfaces consisting of non-porous materials such as glass slides. The immobilised molecules are then employed to react with tagged probe molecules. Fluorescent dyes are used for labelling. This method automatically labels 10000 chemical groups every slide.

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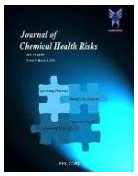

These methods benefit from versatility since the array may be produced in molecular biology labs. The cost of production is quite cheap.[52]

ROCHE Amplichip

Amplichip CYP450, developed by Roche, is the first microarray to be approved for clinical use. It can evaluate genetic changes in the CYP2D6 and CYP2C19 genes. The exam comprises five phases and the analysis requires eight hours. The target genes are first amplified using a polymerase chain reaction (PCR) using gene-specific primers. The enzyme terminal transferase (TdT) is then used to split the amplicons apart and label each of their three ends with biotin. Use is made of the biotin-labeled amplicon once it has been hybridised to the Amplichip DNA microarray.[53]

DNA Microarrays Applications in Drug Discovery and Development

The utilisation of the pharmacological properties of medicinal plants that have traditionally been used to cure a range of diseases is the aim of ethnobotanical-based natural product research. Plants are acknowledged as a source of innovative therapeutic drugs due to their enhanced structural diversity when compared to manufactured chemicals.

New diagnostic indicators, therapeutic response biomarkers, and the mechanisms of action of diverse herbal preparations and phytochemical components have all been discovered as a consequence of the use of DNA microarrays. The identification and validation of new molecular targets is made possible using DNA microarray technology. It is frequently used in preclinical research to predict the harmful effects of herbal treatments. It recognises unprocessed plant parts in their authentic botanical state.[54]

Pure Components

The triterpenoid compounds isolated from the medicinal plant *Centella asiatica* were studied using gene microarrays, and the results showed that Centella triterpenes offer gene-expression response in treating connective tissue diseases such wound healing and microangiopathy. The antiproliferative activities of Coptidis rhizome and its primary component berberine were investigated in human pancreatic cancer cell lines. Patterns of gene expression were analysed using 11000 gene oligonucleotide arrays. The same and different genes might be identified in relation to the anti-proliferative actions of *Coptidis rhizome* and pure berberine.[20,54]

DNA Microarrays in Pharmacogenomics

The DNA microarrays will enable the development of optimised drugs based on different gene expression patterns. Research on genetic polymorphism can be used to classify people according to how effectively they can metabolise medications or how they respond to different illnesses. Xenobiotic-induced gene expression patterns can be investigated utilising oligonucleotide-based DNA chip technology.[55] The microarray genotyping approach may be used to analyse the single nucleotide polymorphisms (SNPs) in genes encoding proteins involved in blood pressure control. The viability of the response to anti-hypertensive medicine is explained by pharmacogenomics.

Recent studies came to the conclusion that metagenomic DNA from faeces samples of different age groups demonstrated antibiotic resistance genes in human gut microbiota using the microarray approach. The study found that different age groups had different amounts of gene types and that as people age, the complexity of the genes encoding antibiotic resistance rises.[56]

DNA Microarray in the study of Herbal Drugs

The use of authentic herbal substances is the first step in assuring the quality, safety, and purity of herbal medications. Arrays based on DNA polymorphism have been developed to identify herbal medicines. In this method, small DNA fragments are amplified using the polymerase chain reaction, and the outcomes are examined using gel electrophoresis and hybridised using species-specific probes. Recent studies have using microarrays to identify therapeutic plants using DNA sequences.[57] The microarray research of gene expression can be used to identify the molecular processes and pharmacological effects of herbal extracts. The patterns of gene expression seen at different phases of the therapy process will assist in the identification of biomarkers with undesirable or prospective repercussions. It will also assist in the identification of fresh therapeutic applications for natural medicines. Microarrays have been used in the drug development

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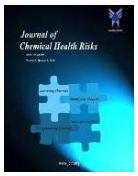

process to select biological targets and lead compounds.[58]

IMPORTANCE AND GOALS

- Pharmacogenomics looks for genetic variation patterns that may then be used to help create the best treatment plans for specific patients.
- For the majority of people, this strategy usually results in the safe and efficient administration of medications.
- More control over the toxicity and effectiveness of drugs.
- A benefit of understanding pharmacogenomics is the potential drop in adverse drug reactions (ADRs).
- If the doctor had been aware of the patient's genetic profile beforehand, many of the fatalities would have been prevented.

BARRIERS TO PHARMACOGENOMICS PROGRESS

Complexity of finding gene variations that affect drug response

Since many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time consuming and complicated.

Limited drug alternatives

If patient have gene variations that prevent them using the drugs, they may be left without any alternatives for treatment.

Disincentives for dug companies to make Pharmacogenomic products

Since it costs hundreds of millions of dollars to bring a drug to market, will pharmaceutical companies be willing to develop alternative drugs that serve only a small portion of the population.

DIFFERENCE BETWEEN PHARMACOGENETICS AND PHARMACOGENOMICS

Pharmacogenetics	Pharmacogenomics
• Single gene • Pathway-based (pharmacokinetics and pharmacodynamics) • Genome-wide association	• Genomics • Transcriptomics and metabolomics • Proteomics

APPLICATIONS

Currently, there are a number of prevalent illnesses that have documented genetic components and high rates of morbidity and death. Their sibling analysis made predictions about the degree of genetic effect on conditions including obesity and diabetes.[59] In a manner similar to this, certain unusual gene mutations can provide a window into the more complex biological processes. For instance, when a patient has extraordinarily high levels of HDL in their blood, it is easy to demonstrate how CETP (cholesteryl ester transfer protein) influences the patient's HDL levels. Another example is a person with a severe mix of immune-deficient conditions and a mutation that deactivates the Janus kinase 3 (JAK 3) genes, since JAK3 inhibition was occasionally predicted to have an effect on human immunological suppression. This led to more investigation utilising pharmacogenetics on drugs that inhibit CETP and JAK3.[60–62] Additionally, the advent of pharmacogenomics has made it feasible to pinpoint the connections between human genes and disease states, enabling the selection of the best therapeutic targets. Many academic institutions and pharmaceutical companies are currently concentrating their research on the association between illness manifestations and genetic variations in order to appropriately categorise diseases.[59,63,64] Although the collection of medical phenotypes associated with DNA samples offers a great opportunity to examine the genetic diversity that occurs in individuals. Genetic variation can be researched by obtaining the DNA of a particular patient. A research that discovered a connection between the phenotypic novel lipase gene family and HDL levels in those who took part in lipid-lowering trials serves as an example of this. The aforementioned research, according to published sources, is supported by a compelling explanation about

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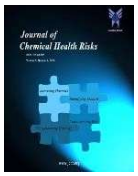

the biological gene selection of candidates. It is straightforward to cross-examine the genome now that it was chosen solely based on phenotypic parameters. These procedures have now replaced over 300000 SNPs throughout the genome by using a small number of haplotype-defining SNPs. Perlegen Sciences has developed novel genotyping methods that can genotype a huge number of hundreds or thousands of markers using high-density oligonucleotide arrays linked to restriction enzyme-based genome reduction. The precise number of SNPs that characterise a particular haplotype is still unknown, despite the advancement of these technologies.

Pharmacogenetics has significantly increased the therapeutic effects and pharmacological application. Patients with a hereditary propensity to negative outcomes may be given low dosages of medicine while being closely monitored. This would probably be advantageous for patients whose VKORC1 genotype has been associated to increased sensitivity to warfarin to progressively start using drugs with limited therapeutic indices like warfarin. Fewer patients are needed for tests thanks to pharmacogenetics, which also lowers the chance of error for many illnesses.[65,66]

Table - 2: Applications of Pharmacogenomics methods in various stages of drug development

Stages	Applications of Pharmacogenomics
Phase I clinical trial	Drug target Identification
	Dose range selection
Phase II clinical trial	Dose modification
Phase III clinical trial	Interpretation of trial results based on pharmacogenetic test results
Phase IV clinical trial	Analysis of reported adverse events with pharmacogenetic tests
Regulatory issues	Requirements for submission of pharmacogenetic data during development by FDA
Patient therapeutics	Personalization of drug therapy
	Pharmacogenetic data in drug labelling
	Identification of responders and non-responders
	Identification of high-risk groups of adverse events

CASE STUDIES

Thiopurine therapy and TPMT (thiopurine methyl-transferase) testing

Thiopurine drug families are used to inhibit the immune system's usual action in the body. These are collectively referred to as anti-metabolites, and they include immunosuppressants like azathioprine and mercaptopurine as well as those predominantly used as an antiproliferative. While 6-mercaptopurine is administered on a regular basis for three to four years to treat paediatric leukaemia, azathioprine, a 6-mercaptopurine prodrug, is used to treat inflammatory bowel disease (commonly known as Crohn's disease). By using TPMT, thiopurine molecules are methylated. S-adenosyl-L-methionine converts into S-adenosyl-L-homocysteine via acting as a methyl donor. As a result, S-adenosyl-L-methionine functions as a derivative and S-methyl as a donor in the mechanism by which TPMT degrades a number of thiopurine-based drugs. Individual differences in drug toxicity and sensitivity are correlated with genetic diversity that largely affects enzyme activity. This enzyme is defective in around 1/300 persons. It has not been determined that TPMT exhibits any phenotypes when not exposed to drugs. For cisplatin-related adverse medication events, such as cisplatin-induced ototoxicity in adolescents, the FDA has recently added TPMT to its list of authorised pharmacogenomic biomarkers.[66,67]

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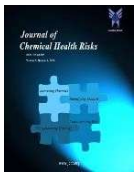

Abacavir therapy and HLA testing

Abacavir is an HIV-1 nucleoside with reverse transcriptase inhibitor, is used to treat HIV/AIDS. Although it is often well tolerated, it occasionally results in mild to severe negative effects include hypersensitivity and lactic acidosis. According to some research, a genetic test or marker can help identify people with HIV who are highly likely to develop severe hypersensitivity reactions brought on by abacavir (around 5% of patients). This hypersensitive response also results in deadly gastrointestinal issues in addition to rashes and fever.[68–70]

The risk to life from this response is quite high, especially if the medication is resumed after being stopped. According to one study, the main cause of hypersensitivity is human leukocyte antigen (HLA) B05701.[45,66] The Australian cohort found that patients had 114 times more HLA-B5701-related hypersensitivity. Nevertheless, research supported by the pharmaceutical industry discovered that individuals with the HLA-B5701 genotype had a 24 times higher risk of experiencing an allergic response. One method to deal with this problem is genetic testing, which integrates pharmacogenetics into clinical practise. The distribution of HLA-B5701 alleles allows for the identification of several populations around the world.[71,72]

Cancer Clinical Trials Optimization and Pharmacogenomics

In order to increase patient survival, clinical trials for cancer must use logical, pharmacogenomic strategies that include precise molecular targeting of cancer cells that are resistant to already available cancer medications. Such revolutionary techniques need to be backed by extensive cancer genomics data, in-depth knowledge of and modelling of the cancer cell's genome, altered cancer signalling pathways, and related epigenetic processes. The DNA sequence of cancer cells' genomes has changed and this has caused all malignancies to develop. These days, it is feasible to compile the whole DNA sequences for a large number of cancer genomes, which would provide important details about how certain malignancies developed in particular people. In terms of clinical trials and cancer research, this marks a whole new stage. The fast growth of unique translational oncogenomic research is due to the employment of exceedingly sensitive and particular advanced technologies, recent scientific advancements, computational tools, and challenging models utilised to address both pharmacological and clinical issues. Now that a substantial number of cancer genomes can be completely sequenced, this information will be crucial for understanding how certain cancers have evolved in particular people. This is a whole new phase in cancer research and clinical trials. The field of novel translational oncogenomic research has grown quickly as a consequence of the use of extremely sensitive and specific modern technologies, current knowledge in the field, computational tools and complex models to address pharmacological and therapeutic issues. During the extraordinarily complex process of carcinogenesis, a number of linked pathways, also known as networks are generated by dynamically interconnected biomolecules in the intercellular, membrane, cytosolic, nuclear, and nucleolar compartments. One such class of signalling systems consists of cell cyclins. Cyclins are typically overexpressed in cancerous cells. Using this as a base, new, rational chemotherapies and cancer chemoprevention techniques can be developed. Cyclins, which are proteins, connect the tumour suppressor gene TP53 and the Thomsen Friedenreich antigen (T-F antigen), as well as Rb, mdm2, cMyc, p21, p27, Bax, Bad, and Bcl-2, all of which play important roles in the carcinogenesis of many cancers. It was realised how important cyclin-dependent kinases (CDKs), their matching cyclins, and CDK inhibitors (CKIs) were. The analysis of cancer models, including CDKs and signalling pathways, in the Nature Preceding raises the possibility of optimising novel clinical trials by developing rational cancer therapies as well as the potential to restore cell cycling inhibition in metastatic cancer cells without leading to transformations that result in drug resistance. On the other hand, a limited number of clinical research concentrating on cancer signalling pathways have produced rather significant advancements in the field of cancer treatment during the past ten years. This is especially true for lung cancer therapies, where several novel anti-cancer drug classes have undergone extensive research and some, like imatinib, have been created utilising rational pharmacology. These anti-cancer drugs were shown to significantly extend the lives of many lung cancer patients. It was shown that several additional drugs used

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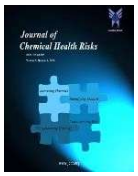

in numerous cancer clinical trials had no appreciable impact on the growth of malignant tumours and hence had no helpful impacts on the treatment of cancer.

The fact that such ineffective or unimpressive drugs are still being researched in several countries' cancer clinical trials nowadays is therefore astounding. Many of these problematic cancers clinical studies are being conducted in a few European countries, and it's conceivable that they aren't being done for the right reasons—as this piece suggests—but just for financial gain. The urgent need for improving cancer clinical trials can only be met by multidisciplinary teams with the capacity to collect the necessary cancer genomics data and validate such individualised cancer genome data with carefully analysed progress of the patients' individualised treatments over time in well-designed clinical trials.

All such optimised cancer clinical (OCC) trials must learn how to manage the drug-resistant malignant tumour subpopulations of cancer patients who have just recently been treated with only modest effectiveness. It is essential to discover the entire, individual cancer genomes present in such therapy-resistant cancer cell subpopulations in order for optimised clinical trials to maximise the survival rates of the cancer patients participating in the OCC trials.[73]

DISCUSSION & CONCLUSION

Pharmaceutical development and drug discovery depend heavily on pharmacogenomics. Over the past 10 years, increased emphasis has been paid to genetic variations associated to the pharmacokinetics and pharmacodynamics of the drug. The development of more specialised therapeutic drugs is the aim of research in the approaching ten years. Not just in the United States and other western countries, but also in Asia, the area of pharmacogenomics is quite well-established. The various health agencies are setting up various data criteria to ensure sufficient pharmacogenomics monitoring. The "International Declaration on Human Genetic Data" was established by UNESCO in 2003. The core principles of the statement have now been followed by all the countries, including China. Phase IV investigations, medication development, and clinical trials may all be carried out with the help of these institutions.

The ramifications of integrating pharmacogenomic testing to stratify patient groups during translational and later stage research may be substantial once a chemical becomes a licenced medicine for a specific condition. The potential clinical advantages of finding a subgroup of individuals who have a superior benefit-risk profile should be considered in light of the cost of any diagnostic procedures required to identify such persons. Using a fictitious pharmacogenomic test, a model has been developed to forecast the predicted financial impact of picking the selected beginning treatment.[28] When utilising several testing techniques, more patients fall into the lower cost categories of the distribution (15% phenotypic prevalence, $200 test fee, simple case). For a typical run of the testing method simulation (74% overall first line treatment efficacy and 60% second line therapy efficacy), the cost savings per patient range from 200 to 767 US dollars (5th and 95th percentile). If pharmacogenomics is economically feasible for clinical usage, it will depend on the cost of genetic variant prevalence testing and the expense of choosing the wrong medicine. Overall the cost of upfront testing for all patients is probably lower than or equal to the cost of other treatment alternatives and the cost of safety concerns that are borne by the portion of patients who are far less likely to benefit for a genetic subgroup of respectable prevalence. In addition to this economic gain, there are unquestionably personal benefits for each patient from a favourable benefit to risk profile after medication. Pharmacogenomics should improve our ability to adapt patient-specific strategies, leading to customised medicines, to better anticipate, prevent, diagnose, and treat diseases.

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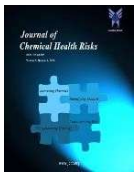

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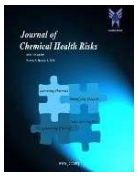

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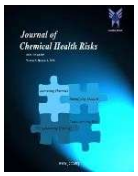

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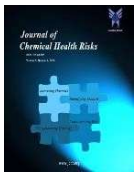

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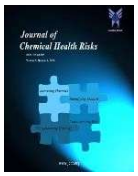

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