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Pharmacogenomics and Personalized Medicine: Understanding Genetic Variations for Safer and Individualized Drug Therapy

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Abstract: Personalized medicine is a new area of medicine that focuses on how genetic differences affect individual response to drugs; called "pharmacogenomics." However, traditional drug treatment involves a "one size fits all" approach that can lead to a lack of response to treatment or undesirable side effects from drugs because of variations in inter-individual response to drugs and drug metabolism. The present review summarizes some of the basic considerations of PG and its role in the safety, efficacy and personalization of pharmacotherapy. It shows genetic differences that are important for the metabolism of drugs, such as single nucleotide polymorphisms, insertions and deletions, and copy number variations, that may change the activity of drug-metabolizing enzymes, transporters, and pharmacological targets. Cytochrome P450 enzymes, such as CYP2D6, CYP2C9, and CYP2C19, and clinically important biomarkers like SLCO1B1, TPMT, VKORC1, and variants of human leukocyte antigen genes are highlighted. Their applications in various diseases – cardiovascular, oncology, psychiatric, infectious and pain – are discussed in representative drug–gene relations with warfarin, clopidogrel, thiopurines and codeine. In addition, this review summarizes the different pharmacogenomic testing models, which are based on genotyping, microarray analysis or next generation sequencing, to enable the identification of clinically relevant genetic variants. Although pharmacogenomics holds significant promise, many hurdles remain as it is not a routine practice, such as costs of testing, lack of clinical knowledge, ethical and privacy issues, and differential access to genomic health. Genotype prescribing and personalised treatment plans could be reinforced by further linkage with EHRs, AI and clinical decision support. Pharmacogenomics, in general, is a promising strategy for improving the selection and dosage of drugs, reducing unnecessary adverse drug reactions, and enhancing the efficacy of drug treatment. Broader use of genetic testing in the routine clinical care of individuals will require continued clinical validation, professional education, and availability of the tests in an equitable manner

Keywords: *Pharmacogenomics; Personalized Medicine; Genetic Polymorphism; Drug–Gene Interactions; Cytochrome P450 Enzymes; Pharmacogenetic Testing; Adverse Drug Reactions; Genotype-Guided Therapy; Next-Generation Sequencing; Precision Medicine.*

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I. INTRODUCTION

The principle of Pharmacology has always been based on "one size fits all", in other words most of the patients receive the same medicines, in the same doses. Drug effects, however, have been shown to be highly dependent on inter-individual variability in drug metabolism, over the last few years with the help of recent advances in the field of pharmacogenomics. All individuals have their own unique metabolism or elimination process of a drug (pharmacokinetics). [1,2]

Therefore, some individuals may benefit greatly from a specific medication while others might not at all or have serious side effects to that same medicine. This variability was traditionally thought to be due to factors that do not involve the genes and include age, body weight, sex, organ dysfunction, diet/drug interactions, but it is now known that genetic factors are a key determinant of drug response. [3,4]

This knowledge has resulted in the development of the field of pharmacogenomics which is the study of how the genes in an individual's genome affect his/her reactions to drugs. A major component within the personalized medicine paradigm is the field of pharmacogenomics which is an emerging model for healthcare using optimized protocols for the individual patient based on his/her unique characteristics rather than using 'one size fits all' protocols. It combines

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genetic, environmental and lifestyle information, culminating in a more accurate translation to clinical decisions taken. [4,5]

It mainly focuses on the study of genetic polymorphisms in the disposition of drugs and the impact of these polymorphisms on drug response. genetic variation may lead to changes in enzyme/protein activity in drug metabolism, drug receptor interaction and intracellular signalling pathways. Specific genetic markers can be used to predict a patient's response to a specific drug, enabling the patient to potentially benefit more from using that drug and finding the optimum dosage for that benefit; optimizing the right dosage for a specific drug to benefit the right patient most. [6,7]

But, today, many therapeutic fields, including cardiovascular diseases, neurological diseases, psychiatric diseases, cancer, pain and infection diseases, have already benefited of its successful applications. In addition, the use of a genetic test is already recommended prior to taking a number of medications by regulatory agencies such as the U.S. Food and Drug Administration (FDA). [8]

While progress has been made, there are still obstacles to the realization of clinical utility of pharmacogenomics in the clinical setting. While significant advances have been achieved, pharmacogenomics is not yet fully integrated into the clinic due to a number of challenges. Therefore, this review will help to provide an extensive overview of pharmacogenomics and the essential part of personalized medicine. The aim of this review is to identify the key genetic variations without which the action of drugs on the body would be difficult or even impossible to manage, discuss the clinical use of the most useful genetic disease markers and the clinical use of these markers as a guide to clinical drug therapy, summarise current regulatory guidelines and address some problems and future possible directions to enable this target of safer and more personalized drug therapy.

II. CONCEPTS OF PERSONALIZED MEDICINE

➢ *Definition:*

The main aim of personalized medicine is to provide the right medicine to the right patient at the right dose. The fundamental objective of personalized medicine is to ensure the right drug for the right patient for the right duration. Hence, PM is defined as "the management of a patient's disease or predisposition using the best available molecular information to achieve the optimal clinical outcome for that particular individual"[9][10][11]

The primary objective of personalized medicine is to enhance the probability of therapeutic effectiveness and reduce the possibility of drug-related toxicity for each individual patient. Pharmacogenomics is considered as one of the key factors that contributes to this concept [12]

➢ *What is Pharmacogenomics in this Concept?*

Pharmacogenomics is the study of how genetic variations in humans influence an individual's response to drugs, mainly focusing on drug metabolism, absorption and distribution. It has been estimated that genetic factors may be responsible for 20 to 95% of variation in drug disposition and effects.[13][14][15][16]

Pharmacogenomics holds great importance for personalized medicine, as different patients show different responses to the same drug. Such differences are often greater among members of a population than within the same individual.[17]

➢ *Traditional vs Personalized:*

Conventional standard methods like 'trial and error', 'one drug fits all' and 'one dose fits all' have major limitations and are responsible for 25-50% of adverse drug reactions or therapeutic failures. The safety of a drug differs from one drug to another, from one person to another, and even from one disease to another [12]

Effective treatment is determined by individual characteristics such as age, gender, disease condition, body weight, and the field of genomics has significantly improved our capability to optimize treatments that are designed for specific patient subgroups or even tailored uniquely for individual patients [18]

Personalized medicine intends to optimize healthcare for individual patients by using predictive biomarkers to enhance therapeutic outcomes and avoid adverse reactions. Considering human complexity, multi-component biomarker panels that include genetic, personal and environmental factors can guide both diagnosis and treatment.[18]

➢ *Best Example - Proof of Concept:*

An illustration of trial-and-error approach versus personalized medicine approach. To obtain the same plasma drug concentration, the dose requirement of nortriptyline varies based on genotype

- Poor metabolizers = 10 mg/day
- Intermediate = 100 mg/day
- Extensive = 100 mg/day
- Ultrarapid = 500 mg/day [12]

PM promises the chance to benefit from the most powerful therapy that targets disease, avoiding toxicity for patients and for payers.

III. FUNDAMENTALS OF PHARMACOGENOMICS GENETIC VARIATIONS

Genetic variation refers to differences in the DNA sequence among individuals. These variations can influence the structure, expression, or function of proteins involved in drug metabolism, transport, drug targets, and immune responses. Consequently, genetic differences can contribute to interindividual variation in drug efficacy, toxicity, and therapeutic response. Pharmacogenomics investigates these genetic differences to support safer and more individualized drug therapy.[19]

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The major types of genetic variations relevant to pharmacogenomics include single nucleotide polymorphisms (SNPs), insertions and deletions (indels), and copy number variations (CNVs).

➢ *Single Nucleotide Polymorphisms (SNPs)*

Single nucleotide polymorphisms (SNPs) are variations involving a change in a single nucleotide/base in the DNA sequence. They are described in the literature as the most common type of genetic variation. SNPs can influence protein function or gene expression and may consequently alter drug metabolism, pharmacokinetics, pharmacodynamics, efficacy, or toxicity.

In pharmacogenomics, SNPs are particularly important in genes encoding drug metabolizing enzymes, transporters, and drug targets. For example, variants in genes such as CYP2D6, CYP2C19, CYP2C9 and SLCO1B1 can contribute to differences in drug response.

SNPs may occur in coding or non-coding regions. Coding-region variants can alter the amino-acid sequence of a protein, whereas non-coding variants may influence gene regulation and expression. Some SNPs can also affect RNA processing or splicing.

For example, the CYP3A422 variant (rs35599367) is an intronic SNP associated with altered CYP3A4 expression and has been linked with differences in statin dose requirements.

➢ *Insertions and Deletions (Indels)*

Insertions and deletions, commonly referred to as indels, involve the addition or removal of one or more nucleotides from a DNA sequence. Depending on their position and size, indels can alter the structure or function of the resulting protein. In coding regions, they may produce frameshift mutations, which can change the reading frame of the gene and consequently alter the encoded protein.

Pharmacogenomic studies have identified clinically relevant indels in several pharmacogenes. The available pharmacogenomic data include indel variants in genes such as CYP2D6, CYP3A5 and NUDT15, with some variants associated with decreased or absent gene function.

Therefore, indels can contribute to variation in the activity of proteins involved in drug metabolism and may affect an individual's response to particular medicines.

➢ *Copy Number Variations (CNVs)*

Copy number variations (CNVs) are genetic variations in which sections of DNA, including whole genes or gene regions, are present in different numbers of copies between individuals. CNVs may involve either duplication or deletion of genetic regions.

CNVs are particularly relevant in pharmacogenomics because changes in gene copy number can alter the amount or activity of a protein involved in drug disposition. A well-known example is CYP2D6, in which gene duplication can result in multiple copies of the gene and contribute to increased CYP2D6 activity. This can influence the metabolizer phenotype and consequently affect the response to drugs metabolized by CYP2D6.

CNV-related changes are also relevant to pharmacogenomic testing. For example, genetic testing approaches have been developed to characterize CYP2D6 variation, while copy-number assessment has also been used in the evaluation of genes such as HER2 in cancer-related applications.

- *Importance of Genetic Variations in Pharmacogenomics*

SNPs, indels, and CNVs can produce differences in gene expression or protein function. These differences may influence drug absorption, metabolism, transport, target interaction, efficacy, and toxicity. Therefore, identification and interpretation of relevant genetic variants can help explain why patients receiving the same medicine and dose may experience different therapeutic outcomes.

The use of these genetic findings in the clinic requires the interpretation of the patient's genotype and the classification into a clinically defined phenotype (e.g. poor metaboliser, intermediate metaboliser, normal/extensive metaboliser, ultra-rapid metaboliser). This information can then be used to inform individual drug choice or dosage, if adequate clinical evidence exists.

In summary, knowledge of various genetic polymorphisms, such as SNPs, indels, and CNVs is a basic pillar of pharmacogenomics and represents the genetic basis for personalized drug treatment.18,20,21]

- *The Function of Drug-Metabolizing Enzymes (CYP450 Family)*

The role of drug-metabolizing enzymes in the pharmacokinetic profile, efficacy and safety of medicines is important. Cytochrome P450 (CYP450) is one of the largest families of drug metabolizing enzymes that includes many enzymes that oxidatively metabolize many therapeutic drugs. Pharmacogenetic polymorphisms may lead to significant inter-individual variations in the metabolism of drugs and therefore affect their response. [4,22,23]

The CYP450 family includes several clinically important enzymes, particularly *CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5.* CYP2D6 is involved in the metabolism of several antidepressants, opioids, and beta-blockers. Genetic variation in CYP2D6 can result in different metabolizer phenotypes, including poor, intermediate, extensive, and ultra-rapid metabolizers. CYP2C9 and CYP2C19 are involved in the metabolism of drugs such as warfarin, phenytoin, and proton pump inhibitors, whereas CYP3A4 and CYP3A5 metabolize a broad range of medicines, including immunosuppressants and statins. [22]

Genetic variation in CYP450 enzymes can alter their expression or catalytic activity, resulting in differences in the rate at which drugs are metabolized. Reduced enzyme activity may cause slower drug metabolism and accumulation of the parent drug, increasing the possibility of adverse effects or

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toxicity. In contrast, increased or ultra-rapid enzyme activity may cause faster drug elimination or, in the case of certain prodrugs, increased formation of active metabolites. This may result in inadequate therapeutic concentrations or altered drug effects. [22,4]

CYP2D6 is one of the most pharmacogenetically important CYP enzymes. Variations in CYP2D6 can influence the metabolism of several drugs used in psychiatry, pain management, and cardiovascular therapy. The clinical significance of CYP2D6 variation is particularly evident when differences in metabolic activity lead to either reduced therapeutic response or an increased risk of adverse effects. [4]

CYP2C19 also shows clinically relevant genetic variation. The presence of reduced-function variants can result in a poor-metabolizer phenotype and alter the metabolism of several drugs, including proton pump inhibitors and other therapeutically important medicines. The CYP2C19 poor-metabolizer phenotype has been associated with increased sensitivity to some drugs because of reduced metabolic activity. [4]

CYP2C9 contributes to the metabolism of several therapeutically important drugs, including warfarin, phenytoin, ibuprofen, naproxen, piroxicam, and tolbutamide. Genetic variants affecting CYP2C9 activity can therefore have important clinical consequences, particularly for drugs with a narrow therapeutic index. Certain CYP2C9 variants have been reported to markedly reduce metabolic activity, which may alter drug exposure and therapeutic response. [4]

The clinical importance of CYP450 pharmacogenomics is demonstrated by the relationship between genotype, metabolizer phenotype, and drug response. For example, CYP2C9 variation is relevant to warfarin metabolism, while CYP2D6 variation can influence the response to several antidepressants and opioids. CYP2C19 variation is relevant to drugs such as clopidogrel and proton pump inhibitors. Thus, identifying clinically relevant CYP450 genetic variants can support individualized drug selection and dosing and may help reduce the risk of treatment failure or adverse drug reactions. [4,22,24]

Overall, CYP450 enzymes form an important link between *genetic variation and drug response.* Understanding the role of CYP450 enzymes and their genetic polymorphisms is therefore an essential component of pharmacogenomics and personalized medicine. Incorporating CYP450-related genetic information into drug therapy can help explain interindividual variability in drug metabolism and support safer and more individualized pharmacotherapy. [4,22,24]

IV. ROLE OF DRUG TRANSPORTERS AND DRUG TARGETS

➢ *Drug Transporters*

Drug transporters play an important role in pharmacokinetics by controlling the movement of drugs across cell membranes and influencing drug bioavailability, tissue distribution and clearance. Genetic variations in transporter proteins can therefore contribute to interindividual differences in drug response.[25]

ABCB1 (MDR1) encodes P-glycoprotein, an important efflux transporter involved in the transport of drugs across the gastrointestinal tract and blood–brain barrier. Genetic variations in ABCB1 can influence drug absorption and penetration into the central nervous system. [25]

SLCO1B1 encodes a liver-specific uptake transporter involved in the hepatic uptake and clearance of drugs such as statins. Genetic variants that reduce SLCO1B1 transport activity can alter statin disposition and are associated with an increased risk of statin-related toxicity. [25]

Transporters can either facilitate drug delivery to the site of action or limit drug access to tissues. SLCO1B1 transports certain statins, including simvastatin, into hepatocytes. Reduced SLCO1B1 activity can alter simvastatin disposition, while the MDR1 transporter encoded by *ABCB1*can restrict drug access to intracellular targets and contribute to drug resistance, particularly in cancer chemotherapy.[18]

➢ *Drug Targets*

Drug targets include *receptors, enzymes and ion channels* involved in the pharmacological action of medicines. Genetic variation in these targets can alter drug sensitivity and consequently influence therapeutic outcomes.[26]

An important example is *VKORC1***,** which encodes the target enzyme of vitamin K antagonists. Genetic variants in VKORC1 can alter sensitivity to warfarin and therefore contribute to differences in anticoagulant response. [26]

In oncology, genetic alterations in *HER2, EGFR, KRAS and BRAF* can influence the selection and response to targeted therapies. For example, HER2 status can guide the use of HER2-targeted treatment in appropriate cancers.[26]

Genetic variation in *HLA alleles* can also influence drug safety. Specific HLA variants, including *HLA-B57:01* and *HLA-B15:02***,** have been associated with severe hypersensitivity reactions to certain medicines such as abacavir and carbamazepine, respectively.[26]

Drug–target interactions are also influenced by genetic variation in genes involved in molecular targets and signalling pathways. Differences in pharmacological target genotypes can contribute to differences in drug effects, although the genetic contribution to many drug targets

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remains more complex and less extensively characterized than that of drug-metabolizing enzymes and transporters.[27]

➢ *Pharmacogenomic Significance*

Overall, genetic variation in *drug transporters and drug target***s** can contribute to differences in drug exposure, efficacy and toxicity among individuals. Therefore, consideration of transporter and target-related genetic variation, together with other pharmacogenomic factors, can help explain interindividual differences in therapeutic response and support more individualized drug therapy.[18]

V. MECHANISM OF GENETIC VARIATION IN DRUG RESPONSE

➢ *Pharmacokinetics – How Genes Affect ADME*

Genetic variations in genes involved in drug absorption, distribution, metabolism, and excretion (ADME) can alter the pharmacokinetic behaviour of drugs. These variations may influence the activity of drug-metabolizing enzymes and transport proteins, resulting in differences in drug concentration, efficacy, and toxicity among individuals [28]

Among the drug-metabolizing enzymes, the cytochrome P450 (CYP450) family plays an important role in drug metabolism. CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 are important polymorphic enzymes. Genetic variants in these enzymes can produce different metabolizer phenotypes, including poor, intermediate, extensive, and ultra-rapid metabolizers. Reduced enzyme activity may lead to increased drug accumulation and toxicity, whereas increased metabolic activity may result in lower drug concentrations and inadequate therapeutic response [22]

Genetic variation in drug transporters can also influence pharmacokinetics. ABCB1 (MDR1), which encodes P-glycoprotein, contributes to drug efflux through the gastrointestinal tract and blood–brain barrier; its genetic variation can therefore affect drug absorption and central nervous system penetration. Similarly, SLCO1B1 encodes a hepatic uptake transporter involved in the clearance of statins, and certain variants have been associated with increased risk of statin-induced myopathy [25]

In pharmacogenomic studies, genes involved in absorption, distribution, biotransformation, and excretion can be selected as candidate genes when investigating pharmacokinetic variation. Drug-metabolizing enzymes such as CYP and UDP-glucuronosyltransferase (UGT) are therefore important candidates for studying differences in pharmacokinetic parameters such as the area under the plasma concentration–time curve (AUC) [29,30]

➢ *Pharmacodynamics – How Genes Affect Drug Action*

Pharmacodynamics describes how genetic variation can alter the interaction between a drug and its biological target and consequently modify drug sensitivity and therapeutic response.

Genetic polymorphisms in drug targets such as receptors, enzymes and ion channels can alter drug sensitivity and therapeutic outcomes. For example, *VKORC1* variants affect sensitivity to warfarin by altering its target enzyme involved in vitamin K antagonism. Somatic mutations in *HER2, EGFR, KRAS and BRAF* can guide the selection of targeted therapies in oncology [26]

The candidate-gene approach for pharmacodynamic studies focuses on genes that interact with the administered drug. For example, for *EGFR tyrosine kinase inhibitors***,** genes in the EGFR signalling pathway, including *EGFR and KRAS***,** can be investigated to determine relationships between genetic variation and drug response [30,31,32]

Genetic variation can therefore influence drug action at the target level even when drug exposure is not the primary source of variability. Pharmacogenomics consequently considers both drug disposition and drug-target interactions when explaining differences in therapeutic response [18]

➢ *Idiosyncratic Drug Reactions and Immunogenetics (HLA System)*

Idiosyncratic drug reactions are unpredictable adverse drug reactions that can involve immune mechanisms. Pharmacogenomic studies have identified genetic factors associated with susceptibility to these reactions. Type B reactions include immune-mediated reactions affecting tissues such as the skin and liver [33,34,35]

The human leukocyte antigen (HLA) system is particularly important in genetically determined susceptibility to severe drug reactions. Specific HLA variants have been associated with severe adverse drug reactions. For example, *HLA-B15:02* is associated with carbamazepine hypersensitivity and severe cutaneous reactions such as Stevens–Johnson syndrome, particularly in susceptible populations [36,37]

A detailed example is carbamazepine. It is primarily metabolized by *CYP3A4* and has been associated with type B, idiosyncratic adverse drug reactions. [38,39] The *HLA-B15:02*allele has been associated with carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis, particularly among Asian populations. Other HLA alleles, including *HLA-A31:01 and HLA-B15:11,* have also been investigated in relation to carbamazepine hypersensitivity [40-42]

Other clinically relevant HLA associations include *HLA-B57:01* with abacavir hypersensitivity and *HLA-B58:01*with allopurinol-related severe cutaneous adverse reactions. HLA-B57:01 has also been reported in association with flucloxacillin-related drug-induced liver injury [43]

Thus, immunogenetic variation in the HLA system can contribute to individual susceptibility to idiosyncratic drug reactions. Identification of relevant HLA variants can help recognize patients who are at increased risk of drug-related adverse reactions [18]

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VI. KEY BIOMARKERS AND CLINICAL EXAMPLES

➢ *Cardiovascular Drugs – Clopidogrel and Warfarin*

Clopidogrel and warfarin are important examples of pharmacogenomic applications in cardiovascular therapy. Genetic polymorphisms in CYP2C19 are major determinants of clopidogrel response because CYP2C19 participates in the metabolic activation of clopidogrel. Variants that reduce CYP2C19 activity can decrease formation of the active metabolite and consequently reduce the antiplatelet effect of the drug. Therefore, CYP2C19 genotype can contribute to differences in clopidogrel response among patients [44]

Warfarin response is influenced mainly by genetic variation in CYP2C9 and VKORC1. CYP2C9 polymorphisms affect the pharmacokinetics of warfarin, whereas VKORC1 polymorphisms influence its pharmacodynamic response. These genetic differences contribute to the considerable variation in warfarin dose requirements between individuals [44]. Thus, CYP2C9 and VKORC1 are important pharmacogenomic biomarkers for understanding variation in warfarin response [12,44]

➢ *Oncology – TPMT–Azathioprine, EGFR and HER2*

Thiopurine drugs such as azathioprine are metabolized through pathways involving thiopurine S-methyltransferase (TPMT). TPMT genetic variation can alter enzyme activity and consequently influence the formation of active thioguanine nucleotides. Individuals with reduced or deficient TPMT activity can accumulate higher levels of active metabolites and have an increased risk of severe haematological toxicity when standard treatment is used. Therefore, TPMT genotype or phenotype can be used to support individualized thiopurine therapy [12,24]

Pharmacogenomic biomarkers are also important in targeted cancer therapy. Genetic alterations involving targets such as EGFR and HER2 can provide information relevant to the selection of targeted therapies. EGFR mutations and HER2-related molecular characteristics have therefore been used as examples of biomarkers that can help distinguish patients who may respond differently to specific anticancer treatments [6,45]

➢ *Psychiatry and Neurology – CYP2D6 and Antidepressants*

CYP2D6 is an important pharmacogenomic biomarker in psychiatric drug therapy because several antidepressants are metabolized through this enzyme. Genetic polymorphisms in CYP2D6 can produce different metabolizer phenotypes and consequently alter drug exposure. CYP2D6 metabolizes several tricyclics.

Antidepressants, including imipramine, nortriptyline, maprotiline, and related drugs, while some selective serotonin reuptake inhibitors are mainly associated with CYP2C19 metabolism. Fluoxetine and paroxetine pharmacokinetics have also been correlated with CYP2D6 genotype [46]

CYP2D6 variation can therefore contribute to differences in antidepressant response. Patients with increased CYP2D6 activity may metabolize certain antidepressants more rapidly and may show inadequate response, whereas patients with reduced enzyme activity may have higher drug concentrations and an increased possibility of adverse effects. Studies have particularly associated CYP2D6 ultrarapid metabolism with non-response to some antidepressant treatments [24]

In neurology, pharmacogenomic drug–gene associations also include CYP2D6-related drugs such as dextromethorphan/quinidine and other neuropsychiatric medicines, demonstrating that CYP2D6 variation can be relevant across both psychiatric and neurological drug therapy [45]

➢ *Analgesics and Anaesthesia – Codeine and CYP2D6*

Codeine provides an important example of how CYP2D6 genetic variation can influence drug response. CYP2D6 converts codeine to morphine, and genetic variation in CYP2D6 produces different metabolizer phenotypes. Poor metabolizers have reduced CYP2D6 activity, whereas ultrarapid metabolizers have increased activity associated with CYP2D6 gene duplication [47]

The pharmacogenomic effect is reflected in the analgesic response to codeine. Reduced CYP2D6 activity can decrease conversion to the active metabolite and may therefore reduce the expected analgesic effect, whereas increased CYP2D6 activity can increase metabolite formation and alter the response and safety profile. Thus, CYP2D6 genotype is an important biomarker for understanding interindividual variability in response to codeine [47]. Codeine is also listed as a CYP2D6-associated drug in pharmacogenomic clinical resources [45]

VII. TECHNIQUES USED IN PHARMACOGENOMICS

➢ *Metabolic and Functional Phenotyping*

Metabolic Probe Testing: Administers a specific probe substrate and measures the ratio of parent drug to metabolite in plasma or urine in vivo and uses analytical techniques to evaluate enzyme activity [49]. They include debrisoquine hydroxylation, dextromethorphan demethylation (CYP2D6); caffeine breath testing, chlorzoxazone 6-hydroxylation (CYP2E1); erythromycin breath testing, nifedipine oxidation (CYP3A4).

Surrogate Tissue Functional Assays: Measures the enzyme function of phase II enzymes (such as SULT1A1 or UGT1A1), using easily accessed peripheral biological matrices, without the need for invasive tissue biopsies [49].

➢ *Gel-Based and Low-to-Medium Throughput Genotyping*

PCR-RFLP (Restriction Fragment Length Polymorphism): First amplifies the polymorphic target region using polymerase chain reaction (PCR); then uses an endonuclease to digest the DNA product and separate the genotypes by fragment size on an agarose gel, such as the CYP2D6*4 splicing defect (Bastin) [48].

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Allele-Specific PCR and Multiplex PCR: Use primers that are specific for the polymorphic sequences which will amplify target alleles without a restriction cleavage site, such as gene duplications found in CYP2D6 ultra-rapid metabolizers.

Oligonucleotide Ligation Assay (OLA): uses two allele-specific probes and a fluorescent-labelled common probe; only the exact sequence match will be joined by thermal DNA ligase, and the products will be separated by fluorescent sequencers [49].

➢ *Mutation Scanning and Conformation Techniques*

Single-Strand Conformation Polymorphism (SSCP): Scans for novel or unknown sequence variants by denaturing PCR products and separating single-stranded conformers in nondenaturing polyacrylamide matrices based on sequence-directed secondary conformations [49].

Conformation-Sensitive Gel Electrophoresis (CSGE) and DGGE: Distinguishes homoduplexes from base-pair mismatched heteroduplexes using mildly denaturing conditions or continuous formamide/urea chemical and temperature gradients [49].

Mismatch Cleavage Assays: Identifies single-base mismatches in reannealed heteroduplexes through targeted chemical modifications (hydroxylamine/osmium tetroxide) or enzymatic cuts (resolvases, T4 endonuclease VII) [49].

Denaturing High-Performance Liquid Chromatography (DHPLC): Employs automated, temperature-modulated column chromatography to separate homoduplex and heteroduplex fragments under partially denaturing states [49].

➢ *Fluorescence-Based and Mass Spectrometric Genotyping*

FRET and TaqMan Allelic Discrimination: Uses dual-labelled fluorogenic oligonucleotide probes (reporter and quencher, e.g., FAM and TET with TAMRA) cleaved by the 5'-nuclease activity of Taq polymerase during amplification, enabling closed-tube, 96-well format SNP detection [49,50].

MALDI-TOF Mass Spectrometry (MS): Characterizes DNA fragments and single-nucleotide differences by precise molecular weight determination using matrix-assisted laser desorption ionization time-of-flight instrumentation without requiring fluorescent or radioactive tags [49,50].

➢ *Microarray and High-Density Array Platforms*

Predefined Targeted PGx Panels: Hybridization arrays containing curated sets of absorption, distribution, metabolism, and excretion (ADME) markers (e.g., Veracode ADME Core, Veri Dose Core, Open Array, DMET, Pharma Oscan, and Axiom Pharmaco focus) to interrogate actionable star-alleles [49,50].

Genome-Wide SNP Microarrays: High-density chips (e.g., Affymetrix Gene Chip, Affymetrix Human Exon 1.0 ST, Illumina Bead Chip, and Illumina Global Screening Array) designed to profile hundreds of thousands to millions of SNPs, copy number variants (CNVs), and transcript-level expression quantitative trait loci (eQTLs) simultaneously [48-50].

Array-Based CNV Calling: Computational algorithms (such as Penn CNV, Quanti SNP, Geno CN, and Nexus) that leverage B-allele frequencies and log R ratios from array signal intensities to detect whole-gene deletions or duplications (e.g., in CYP2D6) [50].

➢ *Next-Generation Sequencing (NGS) and Long-Read Sequencing*

Short-Read Next-Generation Sequencing (NGS): High throughput parallel sequencing (100-200 bp reads) of targeted gene panels (e.g. PGRNseq, PGxSeq), Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) with capture of rare variants, intronic markers (e.g. CYP2C19*17, CYP3A5*3) and novel polymorphisms [51].

Read-Depth CNV Profiling: Bioinformatics algorithms (e.g., XHMM, Conifer, VarSeq and CNVnator) that use coverage depth across short read NGS data to identify deletions and duplications [50].

Linked-Read Sequencing: Reads high molecular weight DNA in short reads, using a partition-based scheme of barcoded gel beads that allows direct haplotype phasing [50].

Long sequencing reads generated by Pacific Biosciences (SMRT sequencing) or Oxford Nanopore Technologies (Oxford Nanopore) that span 6 to 10+ kilobases that can resolve unambiguous haplotype phase, distinguish full-length complex pharmaco genes (e.g., CYP2D6 vs CYP2D7), identify large structural variants, and directly [50].

➢ *Bioinformatic Translation and Clinical Annotation Tools*

In Silico Genotyping and Imputation: Software packages (such as MACH and IMPUTE2) that statistically infer untyped markers and phase haplotypes in candidate-gene and GWAS studies using reference panels (HapMap, 1000 Genomes Project) [51].

Automated Star-Allele Callers: Specialized algorithms (including Aldy, Stargazer, and Astrolabe/Constellation) that analyse BAM/VCF sequencing files to call complex star-allele diplotene's and decompose structural alleles [52].

Pharm CAT (Pharmacogenomics Clinical Annotation Tool): A standardized informatics engine that accepts normalized VCF files, matches identified genetic variants to CPIC-defined star alleles through a Named Allele Matcher, integrates external caller outputs (e.g., CYP2D6 calls from Astrolabe), and compiles individualized prescribing recommendation reports based on clinical guidelines [52].

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VIII. APPLICATIONS IN CLINICAL PRACTICE

➢ *Cardiovascular Pharmacotherapy*

- *Warfarin (CYP2C9 & VKORC1):*

The CYP2C92 and CYP 2C93 variants slow the removal of active S-warfarin, thereby reducing the maintenance dose needed by 20% (1/2), 35% (1/3) or as much as 80% (2/3) to avoid an increased risk of bleeding [54].

One VKORC1 -1639G>A promoter variant reduces enzyme activity, resulting in greater warfarin response. Low maintenance doses are used in homozygous AA (3 mg/day) as compared to GA (5 mg/day) and wild-type GG (6-7 mg/day) [55].

Multi-variable algorithms (such as the IWPC algorithm), combine these genotypes with clinical factors to determine accurate doses for up to 54% of patients, compared with fixed dosing tables [55].

- *Clopidogrel (CYP2C19):*

✓ Loss-of-function (LOF) alleles (2 and 3) reduce the hepatic bioactivation of clopidogrel, leading to high on-treatment platelet reactivity and an increased incidence of major adverse cardiovascular events and stent thrombosis [56].
✓ Gain-of-function (17) alleles cause an ultrarapid metabolizer phenotype, increasing the risk of major bleeding complications [55].
✓ Because dose-doubling strategies fail to overcome platelet non-reactivity in LOF carriers, CPIC guidelines recommend switching these patients to alternative antiplatelet agents like prasugrel or ticagrelor [55].

- *Statins (SLCO1B1):*

✓ The SLCO1B1 521T>C (5) variant impairs the hepatic uptake transport function of OATP1B1, leading to elevated plasma statin exposure and a 17-fold elevated risk of simvastatin-induced skeletal myopathy [54].

High dose (80 mg) simvastatin, dose reduction or alternative less OATP1B1 dependent statins such as pravastatin or rosuvastatin are suggested by the CPIC guidelines [54].

➢ *Clinical Oncology*

- *Thiopurines (TPMT):*

6- mercaptopurine (6-MP) is metabolically activated to generate toxic metabolites.

Functional deficiencies of the enzyme are due to genetic variants (TPMT2, TPMT3A, TPMT3C) [56].

Homozygous deficient “poor metabolizers” (0.3% of people) have toxic metabolites that result in life-threatening bone marrow aplasia [53].

In some clinical situations, physicians can identify patients who are genetically predisposed to receiving 6-MP at the standard dose, and then safely reduce the conversion to 90% to 95% (compromising the dose by only 6% to 10%) of the protocol dose, while maintaining nearly an equivalent therapeutic effect [55].

- *Irinotecan (UGT1A1):*

The active metabolite of irinotecan, SN-38, the very active form, is detoxified by the UGT1A1 enzyme [55].

Polymorphisms (e.g., UGT1A128) affect the ability to do so, and lead to significant systemic toxicities with clinical dose adjustment.

➢ *Psychiatry & Neuropsychiatric Care*

There is high interindividual variation in the response and side effect of psychiatric drugs. High level evidence emphasizes the most important hepatic enzymes, namely CYP2D6 and CYP2C19, for metabolizing most antidepressants and antipsychotics, respectively.

- *Medications Called Selective Serotonin Reuptake Inhibitors (SSRIs):*

✓ CYP2C19 Poor Metabolizers: If given, they may have elevated plasma concentrations of medications such as citalopram and escitalopram, which can lead to marked enhancement in the risk of experiencing drug-dependent adverse effects, including a serious cardiac risk—QT-interval prolongation. Alternatives to treatment (or reduction in dosage by 50%) are suggested.
✓ CYP2C19 Ultrarapid Metabolizers: These metabolize these drugs very rapidly and fail to achieve the desired therapeutic effect. Alternate agents that are not metabolized by CYP2C19 are noted.

- *Tricyclic Antidepressants (TCAs):*

TCAs (amitriptyline) are dual inhibitors with CYP2D6 and CYP2C19. Leaving inadequate metabolizers of either enzyme are at risk for significant, systemic anticholinergic effects. There is no clinical advantage to having an ultrarapid metabolism.

Antipsychotics: (Aripiprazole, Risperidone) CYP2D6 Poor Metabolizers: Dose of aripiprazole should be reduced by 50% to prevent severe extrapyramidal symptoms (movement disorders) and profound sedation [57].

➢ *Infectious Diseases & Antiviral/Antibacterial Safety*

In infectious disease management, pharmacogenomics shifts the focus toward preventing severe, immune-mediated hypersensitivity reactions dictated by human leukocyte antigen (HLA) gene variants.

- *Abacavir (HIV Therapy) & HLA-B*57:01:*

✓ Carrying the HLA-B*57:01 allele creates a near-certain risk for a multi-organ, life-threatening abacavir hypersensitivity reaction.

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✓ Clinical Impact: Pre-prescription screening for this biomarker is one of the most successful PGx standards globally. Genotype testing is mandatory; if a patient tests positive, abacavir is strictly contraindicated.

- *Voriconazole (Antifungal Therapy) & CYP2C19:*

Failure to therapy (subtherapeutic drug concentrations) in CYP2C19 Ultrarapid Metabolizers leads to an increased risk of death. In Poor Metabolizers, the drug is accumulated resulting in high level of Neurotoxicity (Visual hallucinations) and hepatotoxicity. In these extreme phenotypes, CPIC guidelines recommend alternative antifungals (such as isavuconazole, posaconazole).

➢ *Pain Management & Anaesthesiology*

Gene activation pathways are important to the safety and efficacy of opioid analgesics and are essential for post-operative and chronic pain management: hence, PGx plays an important role in the safety and efficacy of opioid analgesics in post-operative and chronic pain management.

- *Codeine, Tramadol, and Hydrocodone (Prodrug Activation):*

These are standard opioids which require bioactivation by the enzyme CYP2D6 for them to become active opioids for example: codeine must be converted to morphine for it to have an analgesic effect.

✓ CYP2D6 Ultrarapid Metabolizers: Experience an exceptionally fast and exaggerated conversion. This causes unsafe spikes in active opioid levels, leading to fatal respiratory depression. (The FDA places a black-box warning against codeine use in paediatric post-tonsillectomy patients for this reason).

Poor Metabolizers of CYP2D6: do not get any reduction from codeine or tramadol as their body cannot bioactivate the drug to help with the reduction of pain. It is recommended to switch these patients to another opioid such as morphine or fentanyl, non-metabolized by CYP2D6 (57).

IX. CHALLENGE AND LIMITATION

➢ *Clinical Implementation and Practical Barriers*

There are very few resources readily available and clinical feasibility barriers which are a real hindrance when adopting pharmacogenomics in routine clinical care, and no clear recommendations on clinical practice. Trainings regarding interpretation of gene-based information and utilizing it in specific management decisions for patients is often lacking and insufficient and relies on inadequate and unconvincing evidence. In addition, the genetic testing results can take time to get which places genetic testing out of the picture for critical logistical decisions as to which medicines to start immediately and urgently.[58]

Study design limitations such as small sample sizes of trials to study a given variant allele in the population heavily restrict the scientific basis of this field. Such disharmony hinders clinical trials from reaching the statistical power needed to deliver an unequivocal, unconfounded result, and makes the medical literature's outcome data pretty much contradictory or hard to replicate. Further traditional pharmacology is based on the incorrect and very limited *one drug-one target* model concept that postulates that the human genome remains fixed for the entire lifespan, contrary to the dynamic environmental influences and complex interactions between networks of organisms.

➢ *Economic, Ethical, Legal and Social Issues (ELSI)*

Societal and economic conflicts exist in the broad-scale integration of personalized medicine and include concerns over patient protection of their identity, informed consent, and systemic discrimination. Patients often don't want to get involved in genetic studies because they think that sharing health information or hereditary disease risk information will result in job loss or no insurance coverage. Equity-wise, the high cost of adapting these specific advanced drugs and diagnostic tests to use in other countries could create barriers to accessing health care and confine access to these advanced drugs to wealthy countries and other exclusive environments, leading to controversial commercially driven race-based medical practice.

X. FUTURE PERSPECTIVES

Pharmacogenomics may also impact on personalized medicine, enabling health care providers to identify the right medication and dosage for each person based on their genetic makeup. Future consideration should be given to implementing pharmacogenomic research results into clinical care in order to enhance the efficacy of treatment and minimize the possibility of medication side effects. Achieving these Practical strategies for incorporating genetic information into care will need to be developed, clinical validations will need to be performed and continued research into goal will be required [61]

The continuing development *of genomic technologies and processing* of data should help in identification of clinically relevant genetic variations. In addition, the next-generation sequencing and targeted pharmacogenomic panels could aid the analysis of more than one pharmacogenetic and artificial intelligence and machine-learning platforms could prove useful for interpreting complex genomic and clinical data. Such advancements would facilitate less generalizable approaches to patient treatment, which need to be validated appropriately to be clinically useful [62]

An additional key priority going forward is integration into clinical practice. Pharmacogenomic information could be integrated into supplemental health records and clinical decision support systems to enable healthcare professionals to detect pertinent gene–drug interactions and to recommend effective dosage. Standardised reporting, adequate genetic testing and ongoing follow-up of results in clinical practice will be key factors for safe and effective implementation [61]

Education, awareness raising, and accessibility will also play a role in the future of pharmacogenomics. There is a need for genetic testing to be appropriately taught to medical and pharmacy students, healthcare professionals and

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patients. Further, there may be ethical issues, genetic information protection issues, cost of testing, and variations in access to healthcare services to be taken into account. Research, health services, laboratories and policy makers working together could enable the development of more sustainable implementation strategies and more equitable access to individualised treatment [61].

XI. CONCLUSION

Pharmacogenomics is the core of the paradigm shift that is occurring in modern therapeutics, from a one size fits all to personalized medicine. The basic knowledge of genetic polymorphisms like SNPs, insertions and deletions, CNVs and their effect on drug metabolising enzymes (CYP450 family), drug transporters and drug targets provide the scientific ground for inter-individual variation in drug response.

Pharmacogenomics is clinically significant due to variation in the activity or induction of the enzymes that are responsible for ADME as well as variations in immunogenetic pathways such as the HLA system, which result in idiosyncratic reactions. This is well demonstrated by the key biomarkers referred to and examples of this, which comprise the bulk of the present review: CYP2C19 for Clopidogrel, VKORC1/CYP2C9 for Warfarin (Cardiovascular), TPMT in Oncology, EGFR and HER2 (Oncology), CYP2D6 for antidepressants (Pezytary/ Analgesics - Codeine).

Technologies such as Genotyping, Next Generation Sequencing (NGS) and Genome-Wide Association Studies (GWAS) have made it accelerate the transition to the clinical practice and also ensure the safety of the medicinal products, decreasing the number of Adverse Drug Reactions (ADRs) that appear when they are used, and increasing the therapeutic effectiveness of the dose, in line with the guidelines issued by the Food and Drug Administration (FDA) and the medicinal products databases such as PharmGKB.

But there are still major challenges such as Ethical, legal and social issues (ELSI), high cost and limited access in developing countries such as India and lack of awareness among clinicians.

With future integration of NGS with Electronic Health Records, AI-driven clinical decision support, and multi-omics approach, pharmacogenomics will become a commonplace clinical practice that will lead to safer, better and truly individualized drug therapy.

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