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Role of Personalized Medicine in Clinical Practice: An Overview of Current and Future Perspectives

Roma Ghai[1], Ashu Mittal[1], Deepali Pandey[2], Md Shamshir Alam[3], Shikha Kaushik[1], Pasha Ishtiyaq[1], Yogita Kaushik[1] and Shardendu Kumar Mishra[1]*

[1]KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, Uttar Pradesh, India.
[2]Faculty of Pharmacy, RBS Engineering Technical campus, Bichpuri, Agra, Uttar Pradesh, India.
[3]Department of Pharmacy Practice, College of Pharmacy, National University of Science and Technology, Muscat, Sultanate of Oman.
*Corresponding Author E-mail:shubham.dr@gmail.com

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Drug administration at similar doses in patients can often lead to various clinical responses. It has been hypothesized that genetics primarily accounts for variation in drug efficacy and toxicity in individuals. Personalized medicine has been a breakthrough achieved by the Human Genome Project which contributes to enhancing quality-based patient care. It deals with the customization of medication considering the distinct genetic and proteomic data that underpins the originality of every patient and every instance of therapeutic intervention. Many cases have shown that inter-individual differences related to drug response can be traced to genetic polymorphism in the gene alleles that codes for metabolizing enzymes, drug transporters, and genetic variations in a person's Major Histocompatibility Complex (MHC). So, the paper throws an insight into epidemiological variations due to genetics, variations in response based on metabolic parameters, and transporters. It also covers genetic variation related to immune-related drug toxicities. Pharmacogenetic testing plays an important role in achieving more precise personalized therapeutics for better public health. The paper discusses various tests for human leukocyte antigen variants and metabolic variants. Every technology inclusion comes with advantages and limitations so personalized medicine also faces certain challenges which are discussed in the paper. Once personalized medicine is used in clinical settings, patients will be able to receive the best medications for them based on their unique genetic and protein profiles.

Keywords: Genetics; Metabolic; Personalized Medicine; Pharmacogenomics; Polymorphism.

The prospective medical and financial achievement of research in drug discovery depends on increased prophecy of drug effects and safety. The approval of new, innovative medicines will be facilitated by focusing therapies on the patients who anticipate benefiting and lowering the threat of adverse effects[1]. Pharmacogenetics, a rapidly escalating field in molecular biology and clinical medicine, will play a crucial role in this transformation. Since 1959, the "pharmacogenetics" word has been in use. Nowadays, with the trend of appending the suffix "omics", numerous research domains have adopted the term "pharmacogenomics", which has been used in many of them. While the former phrase is usually used concerning genes affecting drug

metabolism, the latter is a more generic term that covers any genes in the DNA that could affect how effectively a medicine works[2]. Pharmacogenomics is a branch of science that focuses on identifying the genetic characteristics of an individual that influence how they respond to medications. It's interesting to note that science has progressed to consider hereditary change arrangements in specified people, such as particular ethnic groups, that are responsible for accounting for variation in pharmacotherapeutic effects[3].

The effectiveness of an investigational medicine for patient genotypes and phenotypes can be studied by patient population stratification according to their pharmacogenomic profile. Variations in a gene may affect the pharmacokinetics and pharmacodynamics of a drug, which in turn have an impact on clinical results. Therefore, the idea of personalized medicine represents a significant conceptual shift from the traditional lore of pharmacotherapy, which claims the administration of drugs universally in extensive patient populations rather than smaller subgroups where medications may demonstrate improved effectiveness and ideal safety[4].

Personalized medicine or precision drug is a medical approach in which patient information, based on environmental, lifestyle and genetic factors refers to the healthcare sector to make therapeutic decisions. It is a strategy for treating all patients with the same ailment with tailor-made medication and dosage through molecular diagnostics[5]. Personalized medicine increases patient confidence is cost-effective and will make a difference in the treatment approach[6]. Personalized medicine emphasizes the identification of the biomarkers that help in identifying the clinical signs and indications[7, 8].

Food and Drug Administration (FDA), has acknowledged the need for more clinical data regarding the utilization of biomarkers, has published a list of more than 100 medications since 2007, with pharmacogenomic profile on their labelling and issued a black box warning in multiple of these drugs[9]. To develop new genetic biomarkers and conduct pharmacogenetics research, they are prepared to devote greater resources to these endeavours. More than 20% of the Novel Molecular Entities (NMEs) authorized by the FDA in the United States are classified as personalized drugs according to the Personalized Medicine Coalition's (PMC) report in 2016[10]. These kinds of pieces of evidence (as given below) focus on prevention and early intervention for any disease.

Herceptin is an effective drug for 20-30% of patients having breast cancer. The raised expression of the gene HER2 and its mutations cause patient resistance towards herceptin. So, genetic characterization of the patient having breast cancer can have effective use of Herceptin[11]. The World Health Organization (WHO) has recommended primaquine to cure the liver infection caused by malaria (*Plasmodium vivax* and *Plasmodium ovale*). Primaquine causes hemolytic anaemia, so to eliminate this side effect and bring better therapeutic outcomes, the WHO has issued guidelines to reduce the adverse effect of this drug among patients with Glucose-6-phosphate dehydrogenase deficiency. The discovery of the relationship between antimalarial drugs and G-6-PD deficiency developed a new outlook for a more individualized perspective on the disease[12]. Cystic Fibrosis is a recessive disease that is caused because of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene mutation. In this case, the approach of personalized medicine was performed that was based on the patient's symptoms and genetic traits. Here the supplementation of digestive enzymes was done along with dose adjustment. Many factors were taken into consideration like the patient's physiological characteristics, response to the enzymes, eating habits, etc.[13, 14]. To date, many projects are running as hormone receptor and ribonucleic acid-based molecular diagnosis of breast cancer[15].

In the year 2005, a 15-year research project was funded by the National Institute of Health (NIH) to research into understanding the genetic basis of coronary heart disease, stroke, and breast cancer in correlation to postmenopausal hormone therapy[16]. Another running project is the Personal Genome Project by George M. Church of Harvard University in 2005 to make personal genomes available to the general public. The gathered information is aimed at individualizing ancestors' history, disease risk factors, and biological characteristics[17]. Since the completion of this project, genetic-based variation has been found in the risk factors of Type-2 diabetes, heart

disorders, Parkinson's disease, obesity, prostate cancer, and Crohn's disease[18].

Translational Science is another area of advancement for the individualization of treatment. It stands as the science of transferring preclinical technologies to clinical applications. The methods applied for translational science are like personalized medicine in which the biomarkers are used to envisage potencies and toxicities, the development of animal models to imitate the disease pattern of humans, bioinformatics, and preclinical and clinical analysis to decrease the non-success rate of drug development[19]. These studies bring hope to analyze whether the genetic studies of an individual contribute to making healthy lifestyle choices like proper diet habits and exercising[16]. This article describes the benefits, challenges, and strategies for the execution of an individualized approach to adopting changes in medical practices. Therefore, the objective of this paper is to present a summary of the medications whose pharmacogenomic applications could show their value in predicting pharmacological efficacy, toxicity, and dosage. Several impediments to using pharmacogenomic testing in clinical practice are discussed at the end of this paper.

Epidemiological Variation due to Genetics

Previously, genetic studies influenced the prevalence of disease in communities and have been referred to as genetic epidemiology. This field mainly focuses on the study of familial aggregation of ailment and statistical techniques for family-based gene discovery investigations. Some of the well-researched heterogeneity in response to pharmacological treatment may be explained in part by genetic variances[20]. Numerous factors other than genetics such as ethnicity, race, age, and pregnancy may also be responsible for variations in drug response. Surprisingly, age, gender, and even endemic regional inequalities may manifest as phenotypic effects of distinct epigenetic control. However, genetic pleiotropy and polymorphisms in the targets of pharmacological treatment (such as metabolizing enzymes or protein receptors) and hereditary variations in the metabolism and disposition of pharmaceuticals can have an even bigger impact on the effectiveness and toxicity of medications[21].

Ethnicity

Ethnic or racial groups are the most common categories for people with similar physical characteristics and shared genetic ancestry which may influence therapeutic outcomes[22]. Differences occur due to variations in genes of the genetic germline which are involved in pharmacokinetic and pharmacodynamic is thought to account for 20–30% of drug response variability. The most frequent form of gene disparity in the human genome is called a Single Nucleotide Polymorphism (SNP), and it can function as a genetic markers of population organization and genetic diversity. When the specific SNPs were identified, our comprehension of pharmacogenomics and pharmacogenetics proliferated[23]. Research released in 2011 by Li, Zhang, Zhou, Stoneking, and Tang on the diversity of genes that metabolize drugs in the worldwide population has offered insightful information on the significance of SNP-activated distinction in drug metabolism. This investigation analyzed variation in 283 drug-metabolizing enzymes and transporter genes among 62 diverse racial categories worldwide and established emergence sequences of SNPs in particular populations dispersed globally. These disparities in SNPs play a significant role in the varied medication responses within any population. This research not only supports and explains the genetic polymorphism in drug-metabolizing enzymes, but it also allegedly offers an evolutionary explanation for such variations between ethnic groups[24]. Another research by Sahana has revealed notable variations between Indians and the global population in the gene regularities of clinically relevant pharmacogenetic polymorphisms and they have found the presence of 18 SNP and 34 haplotype variants with HLA alleles which are allied with 85 clinical illustrations among Indians. In India, three variants of the VKORC1 gene (rs9934438, rs9923231, and rs7294) are responsible for the pharmacodynamic variation of warfarin. This genotype information for the VKORC1 gene provides strong support for using optimal doses of warfarin in individual patients before beginning therapy in India. In comparison to the worldwide population, it was discovered that the Indian population had greater allele frequencies for four CYP2D6 haplotype variations. Indians have a noticeably greater prevalence of the abridged function allele CYP2D6*41, which is linked to

a variety of frequently prescribed antipsychotics, opioids, and antidepressant drugs[25].

Pregnancy

Due to the prolonged exclusion of pregnant women from clinical drug studies, there is little information is available about drug levels in pregnant women for various treatments. Now, it appears that this trend is shifting[26]. There have been 264 recorded clinical trials of medications utilized during pregnancy in the past two years, out of which 10.6% describe pharmacokinetic information in the expected mother. This is significant because, according to recent findings, drug concentrations for several treatments, such as antibiotics, antihypertensives, and antiretrovirals, are significantly lower in pregnant women than in non-pregnant controls[27]. This occurs from a wide range of physiological changes which have been extensively documented in Table 1. The Obstetric-Fetal Pharmacology Research Units Network, supported by US-NIH, aims to fill this knowledge gap on pharmacokinetic and pharmacodynamic data during pregnancy[28]. Clinicians can acquire methods for treatment from the contemplation of both mother and fetal genetics and develop curative models. To populate and evaluate the models they will depend on reliable data then only it will be possible to use pharmacogenetics for personalized prenatal medication[26].

Age

Age-related undesirable effects or therapeutic adversity are becoming more common in older people. Significant polypharmacy may play a role in this, which may facilitate the probability of interaction between drug-gene and drug-drug. The precision drug, which is rooted in unique genetic variants, makes it possible to identify patients at risk for unwanted drug reactions and execute individualized treatment plans. It customizes preventative and disease-management measures, including pharmacotherapy, by fusing genomic and genetic information with environmental and clinical aspects. Individualized treatment is made possible by the discovery of genetic variables that affect how well drugs are absorbed, distributed, metabolized, excreted, and function at the drug target level. It is essential to provide methods for the forecast of various phenoconversions that are frequent in older patients along with co-morbidity[29]. However, a single drug's gene interaction is evaluated from the various pharmacogenetic recommendations. A study by Hagstrom identified various single nucleotide polymorphisms in multiple genes that are associated with age-related macular degeneration (AMD). This study offers the groundwork for the hypothesis that SNPs linked to the onset of AMD may influence treatment response. Mainly four SNP rs10490924 (ARMS2 A69S), rs1061170 (CFH Y402H), rs2230199 (C3 R80G) and rs11200638 (HTRA1 promoter), have been continuously demonstrated and found the largest correlations with the onset and development of AMD, and they may also hypothesize to affect therapeutic reaction[30].

Genetic Pleiotropy

When a single gene is responsible for a variety of unique and unrelated phenotypic features is called genetic pleiotropy. This phenomenon is significant to pharmacogenetics because it could undermine the pharmacogenetic relationship[31]. Recent research has demonstrated that genetically supported target drugs, identified by Genome-Wide Association Studies (GWAS) seem to get clinical consent rather than whose targets are not genetically reinforced. That outcome is most pronounced when the gene responsible for the genetic link has been identified (e.g., Mendelian genes), indicating a fundamental issue with the clinical application of GWAS discoveries[32]. According to Finan, 2017, only 4,479 human genes encoded proteins are modulated drugs responsible for therapeutic response out of which only 1,427 are already approved or are being tested in clinical trials as drug targets[33]. Aromatase inhibitors used in breast cancer imply that genetic diversity in allelic association with the pleiotropic CYP19A1 GWAS variation may be associated with improved results in progressive disease, but additional research is needed to confirm this conclusion[34]. Pharmacokinetics-related genes are frequently pleiotropic because they can influence traits, SLCO1B1 and CYP2C19, which are linked to drug transport and metabolism, respectively, are two examples and both are associated with the response of pharmacokinetic profile of anti-platelet agent ticagrelor[35].

Genetic Polymorphism

When the genomic DNA sequences of two individuals are compared, significant sequence variations can be found at various locations

throughout the entire genome. An allele is a gene that is present at any location on a chromosome in two distinct forms, or alternate sequences and this multiple form of a single gene exists in more than 1% population responsible for phenotypic variation is called polymorphism[36]. Individual vulnerability to both dose-dependent and dose-independent adverse drug reactions can be impacted by polymorphisms. Single nucleotide polymorphisms (SNPs), copy-number variants (CNVs), gene insertions and deletions (del), variable number tandem repeats (VNTRs), and premature stop codons are some examples of the various forms of polymorphisms. Both kinetic (e.g. genetic variability of cytochrome P450 enzymes) and dynamic factors (e.g. Drug targets' polymorphism like enzyme and receptors) are prone to determinants[37]. The relationship between the polymorphism and clinical relevance could be determined when the drug and disease should be studied for a specific person. The polymorphism may have an impact on drug dose, effectiveness, toxicity, and pharmacokinetic and pharmacodynamic features; it may also affect a disease's prognosis, and susceptibility, or indeed function as a screening test for specific illnesses[38]. Some examples of clinically relevant polymorphic genes[39] which are associated with drug response are mentioned in Table 2.

Impact of Genetic Variations

Genes influence the expression of proteins involved in the drug ADME, which has an impact on pharmacodynamics. Variation is typically quantitative, meaning that the medicine has a greater or lesser effect or acts for a longer or shorter period. Due to genetic/immunological variations, the effect may have a qualitatively different impact on susceptible individuals.

When genotypic data became accessible, a novel nomenclature was created to describe an individual metabolic rate. Especially diplotypes, which are made up of one maternal and one paternal allele—have been used depicted by a star (*). Each star allele has a unique sequence variation within the gene locus, for example, SNPs may be given a functional activity score when the functional characterization is known, '0' for non-functional, '0.5' for diminished function, and '1' for fully functional. The sum of allelic activity score, which runs from 0 to 3, is most frequently used to define the following phenotypes:

(a) Poor metabolizers are given a score of 0;
(b) Moderate metabolizers score 0.5;
(c) Extensive metabolizers score 1-2,
(d) Ultra-rapid metabolizers score greater than 2.5

Role of Polymorphism of Phase I Enzymes in Response Variation Phase I Enzymes

CYP450 is a superfamily of cytochrome enzymes present mainly in liver cells on the membrane of the rough endoplasmic reticulum and is responsible for the biotransformation of 75% of prescription medicines. Among the various reactions catalyzed by cytochromes are oxidative reactions, dealkylation, aromatic hydroxylation, deamination, and hydrolytic reactions. The maximum drug metabolism is reported in CYP2C, CYP2D, and CYP3A subfamilies. As determined by both clinical pharmacologic investigations and examination of expression in human liver samples, there are significant variations in each CYP's levels of expression between individuals. As a result, variations in drug-metabolizing enzymes can change how various medications interact with the body.

CYP2D6

Up to 25 percent of all pharmaceuticals used in clinical settings, mostly basic medicines including beta blockers, antidepressants, antipsychotics, and opioid analgesics, are metabolized by cytochrome CYP2D6 and it aids in activating various prodrugs. When comparing metabolic capability within and between populations, CYP2D6 exhibits the most phenotypic variability. It is possible to predict therapeutic and unfavourable reactions after administering CYP2D6 substrates using the terms poor, intermediate, extensive, and ultra-rapid metabolizers. The gene that codes for CYP2D6 has more than 100 known alleles. Over 95% of attributes can be explained by just 9 alleles. The CYP2D6 alleles *1 and *2 is fully functional, while *10*17*41 and *10*4*5*6 have reduced function. The response of many drugs alters due to changes in the metabolic activity of enzyme variants.

The opioid analgesic prodrug codeine is accepted for the therapy of pain. Codeine's analgesic activity depends on its conversion to morphine. CYP2D6 is the enzyme that converts codeine to morphine through O-demethylation. Codeine is sufficiently converted to morphine (5–10% of the supplied dose) in patients with normal CYP2D6 activity to deliver the necessary

analgesic effect. While ultra-rapid metabolizers are at a higher hazard for adverse effects such as drowsiness and respiratory depression due to raised systemic concentrations of morphine, poor metabolizers, and intermediate metabolizers are more likely to have insufficient pain alleviation. Constipation and other GIT side effects are less common in poor metabolizers, although sedation and vertigo are common in both. CYP2D6 activity does not affect the antitussive actions of codeine. The Clinical Pharmacogenetics Implementation Consortium (CPIC) advises the application of substitute agents[40].

Ondansetron is an active drug metabolized by CYP2D6 and is given for the treatment of nausea and vomiting, especially post-surgical as well as chemotherapy-induced vomiting. CYP2D6 is prone to deletions, gene duplications, or multiplications. Certain cases reported failure of the therapy and on analyzing the cases, it was seen that the variant was found to be an ultra-rapid metabolizer and have multiple gene copies.

Likewise, the responses of many drugs can vary based on the variation in their alleles. Some examples are depicted in Table 3.

CYP2C9

The most prevalent member of the CYP2C subfamily in the human liver and the enzyme that contributes most significantly to the metabolism of drugs is CYP2C9. The CYP2C9 gene is prone to polymorphisms that result in lower enzyme activity, and this, along with the fact that numerous essential pharmacological substrates have limited therapeutic indexes, raises some crucial questions about the safety and effectiveness of medications. CYP2C9 metabolizes substrates from many drug classes such as nonsteroidal anti-inflammatory drugs (NSAIDs), anti-diabetics, anticoagulants like Warfarin, and anticonvulsants like Phenytoin. Approximately 50 alleles have been defined for CYP2C9 in comparison with the wild-type enzyme (CYP2C9*1), the catalytic activity of two frequent allelic variations of the enzyme is significantly decreased (by less than 10% for CYP2C9*3 and about 20% for CYP2C9*2). Therefore, homozygous carriers of these variant alleles have profoundly impaired metabolism of drugs like phenytoin, glibenclamide, and warfarin.

Warfarin has a narrow safety margin, and its side effects include the risk of bleeding that becomes severe, especially in CYP2C9*3 individuals. The S-enantiomer of warfarin, which is mostly metabolized by CYP2C9 is responsible for most of the anticoagulant action. So, lower dosages of warfarin are required for the tiny subset of individuals carrying the homozygous CYP2C9*3 genotype to achieve the goal of anticoagulation (1 to 1.5 mg once a day as compared to 4 to 6 mg a day for patients with normal genotype). Such persons with increased warfarin sensitivity may have a lower ability to metabolize phenytoin and other drugs too[47]. Below Table-4 summarizes the effects of allele expression with the susceptible drugs.

CYP2C19

Antidepressants, proton pump inhibitors, and antiplatelet medications are among the pharmaceuticals that are known to be preferentially metabolized by cytochrome P450 CYP2C19. Four alleles can explain most of the phenotypic diversity in the highly polymorphic CYP2C19 gene, which has been identified as having over 30 alleles. CYP2C19*1 is the normal fully functional allele, while alleles *1 and *17 have increased function, and *2 and *3 to *8 are non-functional. The major defective allele responsible for the poor metabolizing activity is CYP2C19*2 followed by CYP2C19*3. Asians (30%) are about twice as likely as Africans and Europeans (13%), to have the most prevalent non-functional allele, CYP2C19 *2. Less than 3% of Asians experience *17, although certain Europeans and Africans experience it more commonly (16–21%). Individuals who are homozygous for CYP2C19*1 show a higher metabolism of omeprazole than those homozygous for CYP2C19*17.

In another instance, a thienopyridine antiplatelet prodrug like clopidogrel is indicated to prevent atherothrombotic events. ADP-induced platelet aggregation is selectively and permanently inhibited by active metabolites. About 85% of a dose of clopidogrel supplied is quickly hydrolyzed by hepatic esterase into inactive carboxylic acid derivatives, one of the two primary processes by which clopidogrel is metabolized in the body. The remaining 15%, however, undergoes two subsequent CYP-mediated oxidation reactions (mostly CYP2C19) that result in active thiol metabolites with antiplatelet activity. Variability in response to clopidogrel is linked to genetic

Table 1. The pharmacogenetic liability of usually prescribed drugs during pregnancy

Commonly used drugs during pregnancy	Metabolizing Enzyme	Phenotype Metabolize	Pharmacogenomic liability linked to drug
Metoprolol(Antihypertensive)	CYP2D6	Ultra-rapid metabolizer	Increased Drug Clearance and decreased efficacy
		Poor-Metabolizer	High Plasma concentration is associated with a high frequency of side effects like bradycardia, hypoglycemia in the neonate
CitalopramParoxetineand	CYP2C19CYP2D6	Ultra-rapid metabolizer	Decreased Plasma concentration and potentially elevate the treatment failure
Escitalopram(Anti-depressant)		Poor-Metabolizer	Increased plasma concentration and probably reduced the starting dose by 50%.
Nitrofurantoin(Anti-microbial)	G6PD	Ultra-rapid metabolizer	Risk of hemolytic anaemia
Ondansetron and Metoclopramide	CYP2D6	Ultra-rapid metabolizer	Elevated metabolism of enzymes associated with reduced medication response
(Anti-emetics)		Poor-Metabolizer	Dystonia and other adverse reactions may be increased
Codeine, Tramadol and	CYP2D6	Ultra-rapid metabolizer	Rapid rise in morphine levels in the blood, there is a risk of toxicity, including respiratory depression in both the mother and fetus.
Hydromorphone (Opioid Analgesic)		Poor-Metabolizer	Decreased therapeutic effect

variations in the CYP2C19 gene that diminish the active metabolite's synthesis and, as a result, lower the drug's antiplatelet activity. When taking clopidogrel, people with the CYP2C19*2 allele having loss of metabolic function, are more likely to have significant cardiovascular events, especially if they have acute coronary syndrome treated with percutaneous coronary intervention (PCI). In EMs and UMs, standard starting doses are advised, while in PMs and IMs, CPIC advises using an alternative antiplatelet medication such as prasugrel or ticagrelor[53, 54]. Likewise, the responses of the drugs can vary based on the variation in their alleles as depicted in Table 5.

Table 2. Examples of Genetic Polymorphisms Linked to drug response[39]

Polymorphic gene	Drug	Drug Effect
Drug - Metabolizing Enzymes		
CYP2C9	Phenytoin	Toxicity
	Warfarin	Bleeding Risk
	Tolbutamide and Glipizide	Hypoglycemia
	Losartan	Altered drug response
	NSAIDs	Altered drug response
CYP2D6	Tamoxifen	Toxicity
	Rucaparib	
	Fluoxetine	
	Codeine	
	Beta- blockers	
CYP2C19	Omeprazole	Altered drug response
	Amoxicillin	
	Diazepam	
	Proguanil	
G-6-PD	Rasburicase	Toxicity
	Dabrafenib	
UGT1A1	Belinostat	Toxicity
	Nilotinib	
	Pazopanib	
	Irinotecan	
N-acetyltransferases	Isoniazid,	Toxicity and Hypersensitivity
	Sulfonamides	
	Hydralazine	
	Procainamide	
TPMT	Cisplatin	Toxicity
	Mercaptopurine	
	Thioguanine	
DYPD	Capecitabine	Toxicity
	Fluorouracil	
HLA (Human leukocyte antigen)	Abacavir	Allergic reactions
Drug –Targets		
Angiotensin Converting Enzyme	Lisinopril,	Kidney protective effects,
	Enalapril,	cardiac index, blood pressure,
	Captopril	immunoglobulin A nephrosis
hERG	Cisapride	Torsade de pointes induced by drugs
Potassium channels	Quinidine	Prolong QT syndrome induced by drug
KvLQT1	Disopyramide,	Drug-induced Prolong QT disorder
	Terfenadine,	
	mefloquine	
hKCNE2	Clarithromycin	Arrhythmia induced by drugs

Table 3. Responses shown by allele variants of CYP2D6 for specific drugs

Allele Variant	Drugs Affected	Drug Class	Effect of allele expression	Reference
CYP2D6 *4/*4	Amitriptyline, Clomipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Opipramol	Tricyclic Antidepressant	Risk of toxicity decreased metabolism	41
CYP2D6 *1/*1xN, 1/*2xN, *2/*2xN	Ondansetron	Anti-emetic ($5\text{-}HT_3$ antagonist)	Increased metabolism (therapeutic failure)	42
CYP2D6 *9, 10,17,29,36,41	Metoprolol	Beta-blocker (cardioprotective)	Decreased clearance	43
**3-*8, *11-*16, *19-*21, *38, *40, *42*	Metoprolol	Beta-blocker (cardioprotective)	No clearance	43
CYP2D6 *2, *10, *87, *88, *89, *90, *91, *93, *94, *95, *97, *98	Venlafaxine	Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	Decreased clearance	44
10, 4, 5,6	Venlafaxine	SNRI	Increased concentration in drug level	44
CYP2D6 *1/*3, *1/*4, *1/*5, *1/*6, *4/*41, *6/*10, *10/*10, *41/*41	Tramadol	Opioid analgesic	Increased risk of sedation	45
CYP2D6 *10, *87, *90, *93, *95, *98	Gefitinib	Anti-cancer	Decreased clearance (Gefitinib-induced hepatotoxicity)	46

CYP1A2

CYP1A2 makes up roughly 13% of all cytochrome protein, making it a major metabolizing enzyme in the liver. For CYP1A2, more than 100 substrates have been documented, including numerous clinically significant medications like tacrine, theophylline, clozapine, and endogenous substrates like steroidal hormones.

Since up to 15% of a patient population can be defined as having poor metabolism due to CYP1A2 genetic variation. Moreover, there is a significant racial variation in CYP1A2 activity. As reported, people in Sweden had 1.54 times more CYP1A2 activity than people in Korea, whereas a reduced CYP1A2 activity has been reported in Asian and African populations[62].

Fluvoxamine is a substrate and strong inhibitor of CYP1A2, which results in significant interactions with medications like theophylline, imipramine, amitriptyline, clomipramine, and clozapine that are partially metabolized by this enzyme.

The CYP1A2 gene has been reported to have 177 SNPs, more than 15 variant alleles (*1B to *16), and several subvariants. CYP1A2*1C, *1D, *1F, and *1K have been linked to changed enzyme activity among the polymorphic CYP1A2 alleles that display polymorphism in the promoter region. Although there have been reports of enhanced activity for CYP1A2*1F, this trait is only known to manifest when smoking or consuming large amounts of caffeine.

CYP2B6

CYPB2B6 is considered a minor drug-metabolizing enzyme among all cytochrome enzymes present in the human liver. Artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, and methadone are some of the medications that CYP2B6 metabolizes primarily. The most frequent functionally defective variant, CYP2B6*6 is found in several groups with rates ranging from 15 to over 60%. Due to incorrect splicing, the allele causes decreased expression in the liver. Another significant mutation, known as CYP2B6*18 is primarily found in Africans (4–12%) and does not express functional protein. Although CYP2B6 polymorphism is increasingly being discovered for other drug substrates, it is clinically significant for HIV-infected patients using the reverse transcriptase inhibitor efavirenz.

CYP3A4/5

CYP3A4, the most profusely expressed enzyme in the liver catalyzes approximately ½ of the clinically used medications and oxidizes foreign particles. Inhibition of CYP3A4 will lead to the accumulation of drugs that, on prolonged exposure, can lead to toxicity, and induction will result in reduced efficacy of substrate. Because of CYP3A's large concentrations in both the epithelial cells of the small intestine and liver, it contributes to the pre-systemic metabolic effect after oral drug delivery. When two or more CYP3A substrates are administered, drug-drug interactions involving enzyme inhibition or induction are prevalent. In many cases, the severity of such medication interactions is severe enough to make therapeutic use of the drugs involved impossible.

Cyclosporine, primarily metabolized by CYP3A4 and to a lesser extent partially metabolized by CYP3A5 has been used to avoid complications or rejections after organ transplantation. Polymorphism in CYP3A4 has been shown to decrease the activity of the enzyme, so a low dose of cyclosporine is enough to reach its target levels. Likewise, the effect on substrates by a polymorphism in CYP3A4 and CYP3A5 is summarized in Table 6.

Dihydropyrimidine Dehydrogenase (DPD)

The DPD enzyme, coded by the DPYD gene, is 1st rate-limiting step in the breakdown of pyrimidines and a crucial mechanism for the elimination of fluoropyrimidine chemotherapy medicines. There are three non-functional alleles, with DPYD*2A, *13, and *rs67376798 *2A being the most common. Three fluoropyrimidine medications can be used in clinical settings to treat solid tumours such as breast and colorectal cancer. These are Tegafur, Capecitabine, and 5-fluorouracil (Tegafur is only approved in Europe). After oral administration, Tegafur and Capecitabine are transformed into 5-Fluorouracil in the human body. Only one-to-three percent of the dosage of a prodrug is changed into cytotoxic metabolites like 5-FUMP and 5-FdUMP, targeting cancer cells that also stop DNA synthesis. DPD converts 80% of the drug's given dosage into pyrimidines, which are then excreted in the urine. People with entire or partial DPD deficiency are more prone to experience substantial dose-dependent toxicities like bone marrow suppression, mucositis,

Table 4. Responses shown by allele variants of CYP2C9 for specific drugs

Allele Variant	Drugs Affected	Drug Class	Effect of allele expression	References
CYP2C9 *3/*3	Warfarin	Anti-coagulant	Increased risk of haemorrhage	48
CYP2C9*1/*3	Piroxicam, Aceclofenac, Celecoxib, Diclofenac, Ibuprofen. Indomethacin, Naproxen	NSAID	Increased risk of git haemorrhage	49
CYP2C9 *2 & *3	Glibenclamide, Gliclazide, Glimepiride, Glipizide Gliquidone	Anti-diabetic (Sulphonylurea)	Decreased metabolism (Increased risk of hypoglycemia	50
CYP2C9 *1/*3	Nateglinide	Antidiabetic (meglitinide)	Increased risk of hypoglycemia	51
CYP2C9 *2	Fluvastatin	Anti-hyperlipidemic	Increased concentrations	52

Table 5. Responses shown by allele variants of CYP2C19 for specific drugs

Allele Variant	Drugs Affected	Drug Class	Effect of allele expression	References
CYP2C19 *2	Clopidogrel	Anti-coagulant	Increased platelet reactivity	55
CYP2C19 *1/*17, *17/*17	Warfarin	Anti-coagulant	Increased clearance	56
CYP2C19 *2/*2	Labetalol	Anti-hypertensive (alpha and beta blocker)	Decreased metabolism	57
CYP2C19 *1/*1	Pantoprazole, Lansoprazole, Omeprazole	Proton pump inhibitors	Decreased response	58
CYP2C19 *1/*2, *1/*3	Lansoprazole	PPI	Increased clearance of lansoprazole	59
CYP2C19 *17	Aspirin	NSAID	Decreased platelet reactivity	60
CYP2C19 *2/*2 +*3/*3, *2/*3	Escitalopram	Anti-depressant (Selective Serotonin Reuptake Inhibitor)	Decreased metabolism	61

neurodegeneration, hand, and foot syndrome, and diarrhoea[68].

Polymorphism in Phase II Enzymes

To remove the foreign drug from the human body, phase II enzyme biotransformation reactions frequently conjugate endogenous chemicals, such as acetic acid, glucuronic acid, and sulfuric acid, with different substrates. Transferases make up many phase II drug-metabolizing enzymes. These are UDP-glucuronosyltransferases, N-acetyltransferases, glutathione S-transferases, sulfotransferases, and methyltransferases. About 30% of all metabolites are produced during phase II metabolism[69]. Polymorphic Phase II enzymes may reduce medication elimination and raise the likelihood of toxicities.

Uridine 5 Diphosphoglucuronyl Transferase

The glucuronic acid is conjugated onto tiny lipophilic molecules, such as bilirubin and a wide range of medicinal medication substrates, by the uridine 5-diphosphoglucuronyl transferase UGT1A1 enzyme, which is represented by the UGT1A1 gene. There are more than 30 identified alleles at the UGT1A1 gene locus, some of which result in diminished or eliminated function. Gilbert Syndrome is clinically identified in 10% of Europeans who are homozygous carriers of the *28 alleles, or *28/*28 genotype. Due to a 30% decrease in UGT1A1 activity, such affected people may have 60 to 70% higher levels of circulating unconjugated bilirubin. Owing to decreased biliary clearance, people with the UGT1A1*28/*28 genotype are more likely to experience adverse drug reactions (ADRs) with UGT1A1 drug substrates[70, 71].

Combined with 5-Fluorouracil and Leucovorin, irinotecan, a topoisomerase 1 inhibitor prodrug, is recommended as first-line chemotherapy for the treatment of metastatic colon or rectum cancer. The hepatic carboxylesterase enzyme hydrolyses it into the active metabolite SN-38, which obstructs topoisomerase 1 and ultimately causes the end of DNA replication and cell death. Most therapeutic effects and dose-limiting bone marrow and GIT toxicities are caused by the active SN-38 metabolite. Polymorphism in UGT1A1 renders the metabolite inactive. Due to impaired SN-38 clearance, carriers of the UGT1A1*28 variation are subsequently at increased danger of fatal life-threatening toxicities, like low neutrophil count and diarrhoea[72, 73]. Similarly, comparing individuals with the UGT1A1*28/*28 genotype to those with the UGT1A1*1/*1 genotype, the UGT1A1*28/*28 patients had higher exposure to drug raloxifene and its glucuronides, thus a significantly higher hip bone mineral density[74]. This subset of the population is usually advised lower doses of the drugs as compared to the normal population.

N-Acetyl Transferase and Glutathione S-Transferase

N-acetyltransferases (NATs) and Glutathione S-transferases (GST) make up for around 25% of phase II metabolic activity. N-acetyltransferases are enzymes that catalyze the acetylation of arylamines that are exposed through dietary, occupational, and environmental exposures. Humans have hepatic N-acetyltransferase genetic variants that result in rapid, intermediate, and slow acetylator phenotypes. It has been proposed

Table 6. Responses shown by allele variants of CYP3A4 for specific drugs

Allele Variant	Drugs Affected	Drug Class	Effect of allele expression	References
CYP3A4 *1/*1, *1/*18	Cyclosporine	Immunosuppressant	increased trough concentrations	63
CYP3A4 *22/*22	Lopinavir	Antiretroviral (protease inhibitor)	decreased clearance	64
CYP3A4 *18/*18	Fentanyl	Synthetic Opioid analgesic	decreased dose	65
CYP3A4 *36/*36	Sufentanil	Synthetic Opioid analgesic	decreased concentrations	66
CYP3A4*22	Tacrolimus	Immunosuppressant	Decreased metabolism (overexposure to Tacrolimus)	67

Table 7. Effect of NAT1 and NAT2 allele expression on the substrates

Enzyme	Allele	Drug substrate	Drug Class	Effect of allele expression	References
NAT1	NAT*4	Sulfamethoxazole	Antibiotic	more likely to develop hypersensitivity to SMX	77
	Nat1*3, *14,	Para-aminosalicylic acid	Anti-tubercular	Expressed slow phenotype. Therefore, higher drug exposure.	77
NAT2	NAT2*6A, *6B, *7A, *7B, *14A	Isoniazid	Anti-tubercular	Increased risk of developing toxic liver disease	78
	NAT2*5B	Rifampicin	Anti-tubercular	Increased risk of hepatoxicity	79

Table 8. Effect of GST Mu-1 allele expression on the substrates

Enzyme	Allele	Drug	Drug Class	Effect of allele expression	References
GST Mu 1	GSTM1-Non-Null	Vincristine	Anticancer (Vinca alkaloid)	Development of drug resistance	86, 82
		Busulphan	Alkylating agent	Development of drug resistance and Low clearance	86, 82, 87
		Nevirapine	Antiviral (reverse transcriptase inhibitor)	Steven Johnson Syndrome and Toxic Epidermal Necrolysis	88
	GSTM1 Null	Cisplatin	Anticancer (Platinum-based drugs	Fewer side effects (thrombocytopenia, anaemia, and neuropathy) but Increased risk of ototoxicity.	89, 90
		Cyclophosphamide	Alkylating agent	Fewer side effects (thrombocytopenia, anaemia and neuropathy)	90
		Oxaliplatin	Platinum-based drugs	Risk of developing toxic injury in patients with metastatic colorectal cancer	91

Table 9. Effect of GSTT1 allele expression on the substrates

Enzyme	Allele	Drug/Multidrug therapy	Effect	References
GSTT1	GSTT1 non-null	Cisplatin	Higher likelihood of presenting vomiting and ototoxicity	92, 89
		Busulphan	Low clearance, so higher toxicity	87
	GST1 null	Cisplatin/Doxorubicin/ Methotrexate therapy	Decreased likelihood of progression-free survival in osteocarcinoma	93, 94
		Oxaliplatin	Risk of developing toxic injury in patients with metastatic colorectal cancer	91
		Carboplatin	Risk of developing ototoxicity	95
		Etoposide	Increased risk of lymphocytopenia	96

Table 10. Effect of GSTP1 allele expression on the substrates

Enzyme	Allele	Drug	Drug Class	Effect	References
GSTP1	Ile105Val	Cisplatin	Platinum-based drugs	Higher likelihood of presenting grade 2 or 3 vomiting and lower GFR	92
		Epirubicin	Anthracycline	Good response to chemotherapy and light toxicity in breast cancer treatment.	97
		Cyclophosphamide	Alkylating agent	Stronger progression-free survival	97
	(105)Ile/Ile	Epirubicin	Anthracycline	Good response to chemotherapy and light toxicity in breast cancer treatment.	97
		Cisplatin	Alkylating agent	Less chance of disease progression	92
	(105)Val/Val	Cyclophosphamide	Alkylating agent	Weaker response to chemotherapy and heavy toxicity in breast cancer treatment	97
		Epirubicin	Anthracycline	Weaker response to chemotherapy and heavy toxicity in breast cancer treatment	97
		Cisplatin	Platinum-based drugs	more chance of presenting disease progression	92

Table 11. Altered response of SULT for tamoxifen, an anti-oestrogen

Allele	Drug	Effect	References
SULT1A1*2	Tamoxifen	Reduced metabolism of 4-OH-N-desmethyl-tamoxifen activity, over three times the risk of death in breast cancer patients.	98
SULT1A1*1	Tamoxifen	With higher activity, more likely to have other tumours in addition to breast cancer	99

Table 12. Genetic Variations in Immune System Function

S.No	HLA Gene variant	Suspected Drug	Drug Category	Adverse effect
1.	HLA-B*57:01	Abacavir	Anti-viral	Steven Johnson Syndrome
2.	HLA-B*57:01	Flucloxacillin	Beta-lactam antibiotic	Hepatocytes injury
3.	HLA-B*58:01, 53:01, HLA-A*34:02	Allopurinol	Antigout	Hepatotoxicity
3.	HLA-DRB1*07*01	Ximelagatron	Thrombin inhibitor (now withdrawn)	Increased ALT
4.	HLA-B*1502	Carbamazepine	Anticonvulsant	Cutaneous toxicity
5.	HLA-DRB1*15:01, DRB5*01:01, DQB1*01:02, HLA-B*15:02	Amoxycillin & Clavulanate combination	Antibiotic Combination	Liver toxicity

that an individual's acetylator phenotype may play a role in their propensity to develop specific malignancies linked to arylamine exposures. The two human arylamine N-acetyltransferases, NAT1 and NAT2, are encoded by two genetic variants that are closely connected on chromosome 8. More than 25 polymorphic variants exist for both NAT genes, however, NAT2 null alleles are more common. The sluggish acetylator phenotype is linked to NAT2*5A, NAT2*6A, and NAT2*7A in humans[75, 76]. Due to their slower metabolism, NAT2 slow acetylators are prone to a higher risk of hepatotoxicity, liver damage, and hepatitis brought on by anti-TB medication treatment. NAT1 polymorphisms typically have less interindividual variability and relatively minimal impacts on acetylation function than NAT2 polymorphisms as depicted in Table 7.

Due to the polymorphism of many GST genes, there is a great deal of interest in figuring out whether specific allelic variants affect the risk (or outcome) of several diseases. In humans, there are eight classes of cytosolic GSTs: (GSTA), (GSTM), (GSTP), (GSTT), (GSTZ), (GSTS), (GSTO), and (GSTK). Each class contains one or more homodimeric or heterodimeric isoforms of the protein[80]. The detoxification of electrophilic substances, such as carcinogens, medicinal agents, environmental pollutants, and by-products of oxidative stress, is carried out by the GSTM (a mu class of enzymes through conjugation with glutathione). Genetic variants can alter a person's vulnerability to carcinogens and poisons as well as the toxicity and efficacy of medications. A modest increase in the number of malignancies has been associated with mutations of this class mu gene, most likely because of exposure to environmental pollutants. Mitogen-activated protein kinase (MAPK) signal transduction pathway is modulated by GSTM1, which also regulates apoptosis. While overexpression of the GSTM1 isozyme has been linked to chemotherapeutic resistance, GSTM1 deficiency has been linked to impaired metabolic clearance of carcinogenic chemicals from the body, which may raise the risk of cancer[81, 82].

In ovarian cancer cells, GSTP1 is crucial for cisplatin and carboplatin metabolism[83, 84]. Patients with ovarian cancer may respond

differently to platinum-based chemotherapy due to variations in GSTP1 expression as depicted in Table 8[85].

Thiopurine 5-Methyl Transferase (TPMT)

TPMT is responsible for the covalent binding of a methyl group to heterocyclic sulfhydryl moieties thereby inactivating thiopurine drugs. Though a large percentage of people (86 to 97 percent) inherit two functioning TPMT alleles and have significant TPMT activity, 10 percent of people in Europe and Africa inherit two faulty alleles and have little to no TPMT activity. Genetic polymorphism in the TPMT gene may produce clinical TPMT activity phenotypes, (i.e. high, intermediate, and low) that are connected to different rates of thiopurine drug inactivation as well as risk for toxicities. With just three-point mutations, TPMT *2, *3A, *3B, and *3C, are defined by four non-functional alleles.

Azathioprine (AZT), 6-Mercaptopurine, and 6-thioguanine (6-TG) are the three thiopurine medications utilized clinically. 6-thioguanine is an active metabolite of AZT and 6-MP. To create 6-thioguanine nucleotides, 6-MP and 6-TG are activated by the salvage pathway enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRTase), which is responsible for both bone marrow toxicity and the majority of therapeutic efficacy. As an alternative, 6-MP and 6-TG might be rendered inactive by enzymes Thiopurine methyl transferase as well as Xanthine oxidase, which would reduce the amount of accessible substrate for HGPRTase to activate[62].

Sulphotransferase

The sulfate conjugation of many pharmacologically significant endo- and xenobiotics is catalyzed by the superfamily of sulfotransferase (SULT) enzymes[99]. Neurotransmitters, anti-estrogen steroid hormones, paracetamol and p-nitrophenol are sulfated by SULT1A1. Alleles of SULT1A1 have shown an altered response to Tamoxifen as depicted in Table 11.

Other Enzymes

Glucose-6-Phosphate Dehydrogenase (G-6-PD)

The enzyme is coded by the G-6-PD gene present on the X chromosome and is known to be highly polymorphic. It can detoxify the unstable oxygen species and thus able to produce NADPH and reduced glutathione that play a vital role in the prevention of oxidative damage for RBCs. Following exposure to external oxidative stresses like infection, consumption of fava beans, and therapeutic drugs like primaquine, the enzyme activity in RBCs rises significantly to fulfil the requisite NADPH demand that can prevent the haemoglobin from getting oxidized. However, people with G-6-PD deficiency (i.e. less than 60 percent enzyme activity) are at a greater risk for aberrant RBC destruction, or hemolysis in the presence of oxidative stress180 genetic variants have been identified that have resulted in G-6-PD deficiency. More than 90 percent of variation is in the single base substitutions that alter amino acids, leading to the formation of abnormal proteins with decreased activity. G-6-PD deficiency affects over 400 million people worldwide[100]. Heterozygous males and homozygous deficient females express reduced activity phenotypes.

In individuals with G-6-PD deficiency, Rasburicase therapy has shown a higher risk for severe hemolytic anaemia and methemoglobinemia. Rasburicase is a recommended drug for reducing uric acid levels. The drug converts uric acid into Allantoin, which is a more soluble molecule to be excreted easily from the human body. During this transformation, a by-product hydrogen peroxide is produced which is a highly reactive oxidant. It needs to be scavenged by glutathione to avoid the formation of free radicals. In people with G-6-PD deficiency, glutathione stores are diminished so they are prone to develop higher toxicity if receive drugs like Rasburicase.

Therefore, it's recommended that patients at greater risk (especially individuals of African/ Mediterranean ancestry) must be screened before initiating therapy and that this drug need not be used in patients with G-6-PD deficiency[101, 102].

Genetic Variation in Transporters

Cell membrane transporters are present in different tissues of the intestine, kidney, and liver. They mediate the selective influx & efflux of endogenous substances as well as foreign substances. Transporters as well as metabolic enzymes serve to determine the blood and tissue concentration of drugs and their metabolites. Genetic variations in transporter genes can change a drug's disposition and function, which raises the possibility of toxicity. OATP1B1 is an organic anion transporter encoded by the SLCO1B1 gene and is present on the sinusoidal membrane of hepatic

cells and mediates the uptake of acidic drugs like Statins, Methotrexate, and endogenous compounds like bilirubin from the blood. Approximately 40 SNP's are known that lead to decreased function of transporter.

A common polymorphism in rs4149056 decreases the transport of OATP1B1 substrates in vitro and alters pharmacokinetics as well as pharmacodynamics. The variant displays a change in amino acid that results in decreased expression. It's common in most European and Asian populations[103].

HMG-CoA reductase inhibitors (Statins) are routinely prescribed drugs that effectively lower serum lipid levels to prevent cardiovascular events. The variant rs4149056 in SLCO1B1 increases the systemic exposure of Simvastatin and associated myopathy in a genome-wide association analysis. Therefore, CPIC advises a lower dose of Simvastatin or another statin in such cases[104].

Genetic Variations in Immune System Function

Genetic variation in the human leukocyte antigen system has been implicated as the cause of population-based hypersensitivity reactions. HLA-B, HLA-DQ, and HLA-DR polymorphism among other HLA forms have been linked to several drug-induced hypersensitivity reactions to allopurinol, carbamazepine, abacavir, and flucloxacillin[105, 106, 107].

Abacavir is a prodrug that gets converted to carbovir triphosphate, a reactive molecule that may contribute to Abacavir immunogenicity. Cytotoxic CD8 T cells that have been activated are most likely the mechanism. An abacavir-related peptide may bind to the HLA-B*57:01 protein, according to reports. Genetic testing of HLA-B*57:01 indicators linked to Abacavir hypersensitivity has quickly entered clinical practice due to the significance of Abacavir in therapies. Hypersensitivity reactions can lead to drug-induced liver injury[108].

Among 51 reported cases of liver damage linked to the antibiotic flucloxacillin, a specific genetic variation (HLA-B*57:01) emerged as a risk factor. Researchers further observed that flucloxacillin triggered the activation of certain immune cells (T-cells) which exhibited specific markers (CCR4 and CCR9) and responded by releasing inflammatory molecules (IFN-ã, cytokines, perforin, and granzyme B). Interestingly, a time-dependent binding of flucloxacillin to a protein in the blood (albumin) was directly linked to the extent of T-cell activation, suggesting a potential mechanism for this adverse reaction[109, 110, 111].

Patients with Amoxycillin-Clavulanic acid drug-induced liver injury were shown to have drug-specific T cells, which suggests that the adaptive immune system is implicated in the development of the disease. The antigens produced by Amoxycillin and clavulanate combination and the antigenic determinants that activate T cells were studied using mass spectrometric techniques. Similarly, Isoniazid, Rifampicin, and Ethambutol are among the medications used to treat tuberculosis that can also cause liver damage, which may be associated with HLA polymorphism[109].

Future Perspectives and Challenges to Personalized Medicines

Personalized medicine (PM) is the latest, futuristic, and novel area of research in the field of the healthcare industry. It is an idea in which health care professionals use diagnostic tests to identify specific biological markers mostly genomics, proteomics, and epigenomic profile of an individual to be mindful in providing any sort of treatment to the patient[112, 113]. All such information helps healthcare professionals to target a specific treatment according to the diagnostic results. Resistance to certain treatment strategies for individual patients has led to the urge for more development in this personalized medicine area. Also, the patient goes on one plan of medication and afterwards switches on to another, such practices lead to poorer results, in terms of undesirable effects, drug interactions, or any evolvement or advancement of diseases[114, 115]. Most people are not even aware of Personalized medicine. According to one survey, only 11% of patients became aware of personalized medicine through their doctors[116]. PM has made it possible to diagnose and treat a rapidly growing number of diseases, especially cancer, more precisely than ever before. This practice has empowered doctors to customize the therapy, maximize the effectiveness of drug treatments and minimize their side effects[117]. The main motive of personalized medicine is to provide the "right drug with the right dose at the right time to the right patient"[115].

As of now, personalized medicine has facilitated communication about incorporating genetic diagnostic results into treatment plans, but recent investigations confirm that there is a lack of awareness of implementing this practice. Development in technology brings challenges along with it. We have seen that personalized medicine is a mere basic step toward a more defined approach to patient treatment. It not only prevents the adversities of drugs but also strengthens the preventive and therapeutic efforts of the patient. To combine a personalized medicine approach with healthcare practices, more technologies and diagnostic tools need to be introduced. It is always difficult to get and handle large data of patients. Also, reaching the immediate goal of treating a patient and the end objective of discovering the etiology of the drug with the given data is challenging as well as demanding as it needs real-time analysis and interpretation[118]. The challenge of personalized medicine concerning bioinformatics is large-scale robust genomic data. We can do genomic resequencing through orthogonal resequencing. It is still expensive and time-consuming[119]. The interpretation of the functional effect and effect of genomic variation is also difficult. Calculations and predictions do not provide the pathophysiology of the diseases, so for genetic predictions, experiments are required to be performed which is time-consuming. The analytical methods of single nucleotide polymorphism are limited to the prediction of the impact of mis-sense in it. Also, it is required to analyze the functional region in the genome. So, we can see the major challenge is to develop a method that combines multiple data sources with the inclusion of statistics in it[120]. Many healthcare professionals are not willing to incorporate personal genetic testing into their treatment strategy[121]. Also, there is a huge demand for government agencies to check out the safety of medicines on people in a cost-effective manner. For bridging the slit between the typical medicine system and personalized medicine, already one move has been taken in the USA by passing Genomics and Personalized Medicine Act 2006[122].

CONCLUSION

We have seen personalized medicine start from a profile like genomics, proteomics, epigenomics, metagenomics, etc. to data integration, analysis, and interpretation including Bioinformatics, Biostatistics, and Biomathematics. Every technology inclusion comes with pros and cons and PM is also not different. The main motive of this article is to stimulate the medical fraternity to initiate research in the field of handling and analyzing data and its integration. So basically, personalized medicine is the science of transferring preclinical technologies to clinical applications. The study of personalized medicine brings hope to analyzing whether the genetic habits of an individual contribute to making healthy lifestyle choices. The large data, identification of variants in genomes, and prediction of pathophysiology are still the major challenges. Moreover, it is of the utmost requirement that the concept of personalized medicine should be within the reach of every person, so it should be cost-effective and more approachable in terms of inclusion in normal clinical practices.

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