Review Article

Pharmacogenomics: Generalities and Applications in the Pharmaceutical Sciences

ABSTRACT

Although the main objective of drugs is to improve the person's health, not all people present the same response since it can be exacerbated, adequate, or absent. This variability is associated with gender, age, lifestyle, and therapeutic adherence. Pharmacogenomics studies the genetic variability that influences patients' response to treatment, focusing mainly on the analysis of drug metabolism. This science involves numerous factors. They constitute a network of linked aspects that must be considered to analyze and evaluate the drug response. They can be divided into interindividual variability, pharmacokinetics variability, pharmacodynamic variability, and biomarkers. This knowledge has purposes in various therapeutic areas (immunological, neurological, cardiovascular, and cancer disorders). Therefore, pharmacogenomics has been a key tool in implementing personalized medicine to improve pharmacological response and minimize unwanted effects. Its implementation will increase in the short and medium term, always putting the patient's quality of life first.

Keywords: pharmacogenetics, interindividual variability, pharmacokinetics, pharmacodynamics, biomarkers.

1. INTRODUCTION

A drug is defined as a substance capable of preventing, controlling, or curing the effects that a disease causes in the patient body. This substance can be chemical or biological synthesis [1]. The discovery of drugs has been one of the most relevant historical events for society since they control symptoms and even cure illnesses, which, 100 years ago, caused many deaths worldwide [2]. As a complement, the vaccines have eradicated infections, including polio and smallpox. All this has made it possible to improve society's quality of life [3].

Although the main objective is to improve the person's health, not all people present the same response since it can be exacerbated, adequate, or absent. This variability is associated with gender, age, lifestyle, and therapeutic adherence. However, much of the action generated in the body is provoked by the expression or suppression of genes that encode proteins involved in the drug's pharmacokinetics, pharmacodynamics, and immunological processes [4]. Some products where this phenomenon is observed are:

- Warfarin: a polymorphism in the CYP2C9 gene participates in its metabolism and the S-enantiomer inactivation [5].
- Thiazide diuretics: studies have shown that the presence of polymorphisms in the genes of the Afro-descendant race allows a better response of thiazide diuretics, including hydrochlorothiazide, against arterial hypertension [6].

Through these outcomes, pharmacogenomics was born. This field is a strategy to individualize the selection and pharmacological employment to avoid adverse effects and maximize its efficacy [7], based on identifying genetic variants that influence its pharmacokinetics and pharmacodynamics [8]. Rapid advances in this science have improved the

understanding of adverse reactions, made prescribing more accurate, and reduced unnecessary costs to address such side effects [9].

Pharmacogenomics has become an essential component of personalized medicine [10], which utilizes knowledge of the genetic and molecular basis of health and disease brought on by human genome sequencing to guide decisions regarding disorder prediction, prevention, diagnosis, and treatment [11]. Additionally, it ponders the environment and lifestyle to determine the best way to prevent or treat the condition [12].

Thus, this review aims to identify the application fields of pharmacogenomics in pharmaceutical sciences.

2. PHARMACOGENOMICS CONCEPT, HISTORY, AND EVOLUTION

Pharmacogenomics is an area of pharmaceutical sciences that studies genetic variability in patients' treatment responses, focusing on drug metabolism analysis. The metabolic capacity depends on the production of enzymes, which varies from the polymorphisms found in individuals [13]. Such mutations are genetic deoxyribonucleic acid (DNA) variants in more than 1 % of the world population [14].

Polymorphisms can increase or decrease enzyme synthesis, affecting two essential pharmaceutical processes: pharmacokinetics (the processes that the body performs on a drug) and pharmacodynamics (the effects that the drug has on the body) [13, 15]. Therefore, the principal objective of pharmacogenomics is to predict an individualized drug treatment based on each person's genetic profile based on a genome study [16].

Likewise, it is necessary to distinguish between pharmacogenetics and pharmacogenomics. The first refers to interindividual variability in drugs under genetic factors' influence. The second concept encompasses the interindividual variability of such drugs under the influence of certain gene expressions, which may also be fundamental in the physiopathological manifestation [17].

The historical pharmacogenomics bases arise from James Watson and Francis Crick's elucidation of DNA structure in the 1950s [18]. This finding laid the foundations of modern molecular biology and the branches of science associated with genetic material study.

Subsequently, another landmark event was the Human Genome Project in the 2000s. The aim was to complete a mapping of human genes to obtain their functional, physical, and chemical composition [19].

In this way, in the post-genomic era, research began with the contribution of omics. These sciences allow the study of diverse molecules participating in the organism's functions. They include proteomics, metabolomics, and genomics. Proteomics studies many proteins in a sample, covering their functions, post-translational modifications, and interactions with other proteins or substances [20].

Metabolomics analyzes the concentration changes of specific metabolites according to the body's responses to genetic variation. It also allows for obtaining a sample metabolic profile, both qualitatively and quantitatively [20].

Finally, genomics is dedicated to investigating the complete genome. It allows studies of gene identification, characterization, interaction, and function [20].

Thanks to human genomics studies, interest in pharmacogenomics awoke to explain the illness from a genetic basis. Besides, it intends to search for new therapeutic targets and drugs [19].

Pharmacogenomics has two clinical methodologies: candidate gene analysis and genome-wide association studies. The first strategy is identifying the genes responsible for drug metabolism, transport, or therapeutic targets and ruling out possible polymorphisms that affect these processes. Regarding the second, a comparison is executed of the total genomic profile of two groups of patients phenotypically classified into the one that receives the drug and the one to which the placebo is administered. Both are genotyped, and the frequencies are compared to uncover polymorphisms affecting pharmacological response [21].

The candidate gene analysis has made it possible to understand the pathologies. In an investigation, genetic mapping was done to identify a mutation that causes autoimmune myasthenia gravis in seven family members: four affected, two unaffected, and one with an uncertain diagnosis. The results indicated that a sequence variant in the ENOX1 gene is related to the probability of suffering from it in said individuals [22].

Furthermore, genome-wide association studies have identified genetic variations that influence cancer risk. It has been determined that specific alleles increase the hazard. Many are located in non-coding regions, which influence gene expression. Such information has led to the discovery of new drugs and the repositioning of existing ones [23].

3. PHARMACOGENOMICS IMPORTANCE

Pharmacogenomics is gaining relevance in pharmacological research due to non-invasive genetic engineering and molecular biology techniques, recombinant DNA, and the need to explain drug response variations [16, 24]. Researchers aim to find biomarkers associated with the diagnosis, prognosis, and treatment response [24].

The identification of genes with polymorphic variants has had a significant clinical impact. An example is warfarin, an anticoagulant indicated to prevent and treat thromboembolic events. Its correct dosage is difficult because of the narrow therapeutic index, causing bleeding and response variability in patients [25]. The polymorphism in the CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes influences their therapeutic effects, demonstrating that they are associated with an increased risk of excessive anticoagulation and bleeding events [25, 26].

The major histocompatibility complex (MHC) comprises a group of cell surface proteins that bind to foreign molecules to be recognized by the corresponding T lymphocytes, thus inducing an immune response. This protein structure is the human leukocyte antigen (HLA) [27].

Variation in HLA genes defines susceptibility to autoimmune diseases, infections, and immune reactions [27]. HLA-B*57:01 gene carriers have a high-risk factor for hypersensitivity to abacavir [24, 26, 28]. It is a first-line antiretroviral, classified as a nucleoside reverse transcriptase inhibitor, against human immunodeficiency virus (HIV), capable of terminating DNA synthesis and, therefore, viral replication [28]. Its administration in this group can trigger Stevens-Johnson syndrome (SJS) and toxic epidural necrolysis (TEN) [29].

Both are hypersensitivity reactions (HSR), which are excessive or inappropriate immune responses produced by the immune system to a self or foreign antigen, damaging body tissues. According to the mechanism of tissue injury, HSRs are divided into four types [30, 31], as shown in **Table 1**.

Table 1. Types of hypersensitivities and their main characteristics [30, 31].

Hypersensitivity type	Characteristics
Type 1 HSP	-It is an immediate immune response mediated by specific immunoglobulin E (IgE) against the triggering agent. -This reaction can be acute, resulting in severe systemic complications, or chronic, comprising recurrent processes, but not so severe.
Type 2 HSP	-It is mediated by IgM and IgG antibodies, which use cell surface antigens. -Cytotoxic reactions that produce cell destruction, opsonization, and phagocytosis are developed.
Type 3 HSP	-IgM and IgG antibodies bind to the antigen, forming immune complexes. -The complexes are deposited in various tissues, causing an inflammatory reaction.
Type 4 HSP	-Delayed type reactions are observed (the response is reflected 48 to 72 hours after the immune reaction). -They are mediated by T cells.

SJS and TEN are considered type 4 HSR to drugs and their metabolites. They represent distinct grades of the same severe skin adverse reaction, characterized by widespread keratinocyte death. It results in the denudation of the skin and mucosa to total thickness, making the person susceptible to sepsis. Mortality is around 30 % [32, 33, 34].

Given this situation, the United States Food and Drug Administration (FDA) established the mandatory exam for HLA-B*57:01 in all people to be treated with abacavir. Similarly, it indicated its prohibition in those with positive results for this genotype [35].

The same happens with carbamazepine, a tricyclic antidepressant against epilepsy and other neurological and psychiatric disorders. Its mechanism is unknown but associated with binding to sodium channels and interactions with calcium channels. Moreover, it potentiates the inhibitory effects of gamma-aminobutyric acid (GABA) and decreases the glutamate excitatory [36].

The presence of the HLA-B*15:02 allele is associated with an augmented risk of HSRs with severe cutaneous involvement, including SJS and TEN, particularly in Asian persons [37, 38]. The FDA changed the drug's label, incorporating information on allele genomics as a marker, and recommended genotyping in this population [37].

In transplant patient care, polymorphisms in the ABCB1, CYP3A4, and CYP3A5 genes are recognized and considered to optimize tacrolimus therapy [39]. This therapeutic option has favored patient survival after transplantation. It forms a complex with the immunophilin FK binding protein 12 (FKBP-12), interfering with the transduction pathway of the intracellular calcium-dependent signal essential for T lymphocyte activation [40]. Its indication has spread as a first-line option for intestine, kidney, heart, lung, and bone marrow transplantation [41] since adequate immunosuppressive therapy is essential to maintain high allograft viability and prevent acute rejection [39]. Nevertheless, genetic factors influence absorption, metabolism, excretion, and drug response [41].

Because of these findings, the FDA recognized that pharmacogenomics plays a critical role. Now, pharmaceutical products can contain information on genetic biomarkers [39]. Labeling aims to provide information to patients and health personnel on the proper use of the product and to facilitate its understanding. It is a tool in health education and is referenced every day in practice by health professionals [42].

An extensive list of therapeutic medications with pharmacogenomic information on their respective biomarkers has been created [43]. Thus, this science has found an application field in therapeutic areas such as psychiatry [16, 24], analgesia [24], neurology [16, 24, 45, 46], oncology [16, 46], and cardiology [16, 24, 47].

4. FACTORS AFFECTING PHARMACOGENOMICS

Pharmacogenomics involves diverse factors. They constitute a linked network, which must be analyzed and evaluated for the drug response. They can be divided into interindividual variability, pharmacokinetics variability, pharmacodynamic variability, and biomarkers. Each is detailed below.

4.1 Interindividual variability

Everyone is a complex organism involving factors and aspects of relevance in clinical practice. Each individual responds singularly to various treatments or the same disease. This differentiated response is mainly the product of intrinsic drug, genetic, epigenetic, environmental, and personal factors. Together, they affect the proteins that metabolize or transport substances, their therapeutic targets (receptors), and variations in relevant metabolic enzymes. The result is the influence on efficacy and pharmacological safety. Nonetheless, the relevance or contribution of each one varies for the substance under study [24].

According to the above, there are factors related to the drug. Some are physicochemical characteristics, administration routes, dosage, excipients, and interactions with other medicines [24, 48].

Concerning genetic factors, metabolic enzymatic activity, transporters' efficiency, and some receptors' sensitivity must be considered [24, 49, 50]. The interindividual variability in the expression of the genes of drug-metabolizing enzymes such as cytochromes (CYPs) and some transporters is more remarkable than other types [51].

Another component is epigenetic factors. One of them involved histones, proteins that, when undergoing modifications such as methylation or acetylation, favor the alteration of gene expression [52].

Expression levels are associated in the same way with micro-RNAs (of ribonucleic acid) since their role in regulating the expression of drug metabolism and transport genes has been identified [53]. As a complement, DNA alterations such as methylation in regions rich in guanine and cytosine are frequently found in the gene promoter region, causing its silencing [54].

Likewise, environmental aspects affect the differentiated response between patients. They include smoking, alcohol consumption, and diet [24].

Finally, the elements of the person must be pondered. They incorporate age, sex, pregnancy, lactation, renal and hepatic functions, and pathologies [24]. A decline of up to 3.5 % in the ratio of CYP enzymes has been seen for each life decade, as well as a reduction in renal function. Additionally, delayed gastric and colonic emptying has been reported in women, together with a higher stomach pH [55]. Together, these characteristics significantly vary the pharmaceutical product response.

4.2 Pharmacokinetics and pharmacodynamic variability

The genetic variability of populations and individuals significantly affects other pharmaceutical processes in the human body, such as pharmacokinetics and pharmacodynamics [56]. These sciences oversee studying the interactions and mechanisms of action of drugs within the organism [57]. Regarding pharmacokinetics, the variability of the drug absorption, distribution, metabolism, and excretion (ADME) process is being investigated [58].

Metabolism is interesting because polymorphisms in the genotypic sequence encoding for metabolizing enzymes or transporter proteins can cause unequal therapeutic responses among individuals. When this happens, problems in the safety and efficacy of pharmaceuticals can arise [57, 59].

The genetic variants involved in pharmacogenomics can be somatic or germinal. The somatic ones occur in the individual after birth and are not hereditary. They optimize the most effective therapeutic choice for the patient [57, 60]. In contrast, the germ cells are hereditary, acquired from the parents, with the consequent progeny transmission. They make it possible to predict therapeutic efficacy and toxicity [57, 60]. These variants are notable because the genes have all the information to synthesize proteins, and, in case of changes in the sequences, they can decrease or increase their function, such as drug transport or metabolism [57, 61].

Pharmacogenomics aims to create a relationship with pharmacokinetics for drug dosage personalization. This synergy seeks to improve its benefits and reduce consumption risks [60].

The CYP450 family is among the metabolizing enzymes responsible for 90 % of the hepatic metabolism of endogenous and exogenous substances. Thanks to pharmacogenomic studies, four metabolic phenotypes responsible for the medicine concentration in circulation have been identified [62], detailed in **Table 2**. This classification has helped to identify people who suffer from substance poisoning, even when administered at regular doses [63].

Table 2. Definition of drug metabolic phenotypes [62, 64].

Type of metabolizer	Definition
Ultrarapid	Due to two active copies of the CYP450 gene, it has a high metabolizing capacity. Therefore, the minimum effective concentration and therapeutic response are never reached.
Rapid or normal	It has two phenotypically active alleles, one active and one partially defective, or a null allele and a duplication. It has an adequate response because it reaches the desired concentrations.
Intermediate	It has two alleles in diverse combinations: defective-defective, defective-null, or active-null. The defective one causes the enzyme to reduce its metabolizing function, and the null one does not work. These conditions reduce metabolic capacity, and the plasmatic concentrations slightly exceed the minimum toxic concentration, adversely affecting the organism.
Poor	It has both null alleles or a deleted gene (loss of one or more nucleotides of the genetic material). Its metabolic capacity is nil, and the plasmatic concentrations greatly exceed the minimum toxic concentration, predisposing it to side effects on health by drug accumulation.

For its part, pharmacodynamic variability depends on how the drug-receptor interaction is carried out. Therefore, genes that encode for receptors and functional proteins related to pharmacological actions after receptor binding are studied. If a subject has polymorphisms, the therapeutic response may be improved by encoding more therapeutic targets or diminished by encoding less. In addition, studies indicate that there are more receptors than usual, and there is a greater possibility of developing adverse reactions. The drawback is that the phenotypic manifestations of polymorphisms in genes related to pharmacodynamics are only observed when the patient is exposed to the substance [13, 62].

4.3 Biomarkers

Pharmacogenetic or pharmacogenomic biomarkers are genes responsible for encoding proteins involved in the action of drugs, either by participating in the mechanism of action or their metabolism, often related to pharmacological toxicity. Its variations have allowed the description of interindividual and interpopulation responses, transforming as a vital tool in implementing personalized medicine to improve the pharmacological response and minimize unwanted effects [16].

Genetic variation is the product of structural differences in particular genes or variations in portions with regulatory activity, the product of insertions, deletions, duplications, inversions, or substitutions of nitrogenous bases modifying the DNA sequence. This situation generates a change in the gene functionality, with the consequent synthesis of modified proteins [65].

Each gene occupies a characteristic location on a specific chromosome and has components necessary for transcription regulation. They include exons, introns, promoter sequences, and regulatory regions [66].

The exons are segments with information that encodes the macromolecule, while the introns comprise sections that do not appear in the mature mRNA because they are removed. Regulatory regions can silence or amplify gene expression, and the promoter indicates the transcription initiation [66].

Polymorphisms can occur as single nucleotide polymorphisms (SNPs), representing about 90 % of all variations found in the human genome. Other more complex differences are copy number variations (CNVs) [65, 67].

SNPs occur when a paired base pair is substituted within the nucleotide sequence. If the variation is in a regulatory area or gene, it can alter the encoded protein synthesis [65].

For its part, CNV occurs when DNA sections are repeated or deleted several times. As with SNPs, they become transcendental when they affect regulatory or encoding regions. The result could be increased protein synthesis, which could lead to an augmentation in enzymatic activity, with the consequent affectation of drug metabolism and alteration of pharmacokinetic parameters. On the contrary, it could cause gene deletion, and since there are fewer protein copies, the enzymatic activity could be diminished [68].

Studies have indicated that allelic variations of pharmacogenetic biomarkers occur with different population frequencies according to ethnicity, age, and gender. Such research has generated a more personalized medicine capable of tailoring treatment to individual needs and patients' characteristics. A current advantage is the technological improvements in determining pharmacogenetic biomarkers [69, 70, 71, 72]. **Table 3** lists some of those studied together with drugs associated with each other and the clinical area where these medications are used.

Table 3. Pharmacogenomic biomarkers associated with different drugs utilized in clinical practice for distinct therapeutic areas.

Biomarker	Drug	Therapeutic area
CYP2C19	Formoterol [73]	Pulmonary
	Carisoprodol [74]	Rheumatology
	Citalopram [74]	Psychiatry
	Clopidogrel [74]	Cardiology
	Diazepam [74]	Neurology
	Voriconazole [74]	Infectious diseases
CYP2C9	Celecoxib [75]	Rheumatology
	Meloxicam [76]	Anesthesiology
	Phenytoin [76]	Neurology
	Piroxicam [76]	Rheumatology
	Warfarin [77]	Hematology
CYP2D6	Tamoxifen [78]	Oncology
	Venlafaxine [79]	Psychiatry
	Tramadol [80]	Anesthesiology
	Propranolol [81]	Cardiology
TPMT	Azathioprine [82]	Rheumatology
	Cisplatin [83]	Oncology
	Mercaptopurine [84]	Oncology
	Tioguanine [84]	Oncology

VKORC1	Warfarin [77]	Hematology
CYP1A2	Rucaparib [85]	Oncology
UGT1A6	Valproic acid [86]	Neurology
EGFR	Cetuximab [87]	Oncology
HER2	Trastuzumab [88]	Oncology
HLA-B	Carbamazepine [89]	Neurology

5. CLINICAL APPLICATION OF PHARMACOGENOMICS

Table 3 illustrates the importance and variety of application areas of biomarkers in understanding the response of numerous drugs on the market. This information has caused important official agencies such as the FDA to show interest in data collection that serves as a guide and highlights the importance of biomarker analysis prior to decision-making associated with the therapeutic indication and its respective justification [90, 91]. Some of these areas are explained in more detail.

5.1 Immunological disorders

HSRs and autoimmune problems affect a significant percentage of the world's population. HSRs occur from an exacerbated immune response against allergens from the environment, while autoimmune pathologies develop when the immune system triggers a response against autoantigens. Both arise from a loss of clinical tolerance and reaction against innocuous foreign or self-antigens. For this reason, at the therapeutic level, the aim is to broaden the activation threshold of the cells and to modify the function of antigenic memory T and B lymphocytes to restore tolerance to some degree and avoid symptoms for an extended period [92].

Conventional therapy included nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressants. These molecules are non-specific and have serious adverse effects, which can even worsen the patient's health [93]. For example, glucocorticoids can provoke Cushing's syndrome by increasing cortisol in the blood. Its manifestations comprise edema, weight gain, and striae [94].

These drawbacks changed with the advent of antigen-specific immunotherapy. It involves drugs capable of decreasing the immune response against a particular antigen or a set of antigens associated with an immune disorder [95].

This therapy has shown promising results, and its effectiveness against rhinitis, conjunctivitis, and asthma has been appreciated. Gradually increasing amounts of the allergen responsible for the clinical picture are administered subcutaneously until the patient reaches a dose that promotes immunological tolerance against this element [96].

In addition, genetic factors associated with HLA confer a greater risk of autoimmune liver affectations. These molecules induce and regulate the immune response through antigen presentation and T-cell recognition. For this reason, a therapy capable of promoting tolerance through the gradual administration of an antigenic peptide of synthetic origin is being studied [97].

Antigen-specific immunotherapy can change the natural course of immunological illnesses. Moreover, pharmacogenomics can monitor clinical evolution and predict treatment-effective responses, select patients who respond to them, facilitate the study of drug combinations, investigate optimal doses, and discover the mechanism of action in detail [92].

Therefore, biological therapy, targeting immune system components, is attempted as a better replacement. The problem is that not all patients respond adequately. Some do not have a response or lose it after having responded [93].

Therefore, pharmacogenomics locates genetic determinants involved with the efficacy or toxicity of the therapeutic options available against these conditions, making finding the best therapeutic route possible. One of the investigations regarding genetic polymorphisms and the clinical response to treatment of systemic lupus erythematosus (characterized by the generation of antibodies against organs and tissues) revealed their presence in genes concerned with pharmacokinetics such as CYP450, the organic-anion transporter polypeptide (OATP), and ABC transporters, and pharmacodynamics, specifically the Fc gamma receptor (FcγR) and toll-like receptors (TLR) [98].

These variations affect the therapeutic target and the patient's sensitivity to the drugs, respectively. For this reason, its knowledge is key to reducing the risk of suffering secondary reactions and even favoring the treatment efficacy [98].

On the other side, identifying the genes corresponding to disease susceptibility, therapeutic targets, drug metabolism, and genetic predictors with similar pathogenic signaling pathways are excellent candidates for improving therapeutics [93]. One case refers to the expectation of the pharmacological response against tumor necrosis factor alpha (TNF-α) through evaluating the genetic variants of its signaling pathways [99].

In a bibliographic study, several polymorphisms involved in the mechanism of action of anti-TNF-α therapies for rheumatoid arthritis were described, mainly six associated with infliximab, five with etanercept, and three with adalimumab. They are responsible for preventing the blockade of the interaction between TNF-α and the binding sites of its cell surface receptors (p55 and p75) [100].

Also, it is possible to identify genetic factors that stimulate the probability of triggering enzyme activity descent, leukopenia development, and HSR generation when consuming some anti-inflammatory or immunosuppressive drugs [101]. Even associations with HLA-encoded MHC genes have been accomplished [102].

Candidate gene and genome-wide association studies have been valuable in identifying elements related to allergic reactions' susceptibility to various medications since the HLA genes encode proteins presenting antigens to T lymphocytes, which may be predictors of HSR. It was demonstrated through a study on a population from Taiwan, which experienced carbamazepine-induced SJS. Candidate gene analysis embraced the genotyping of HLA alleles and CYP450 polymorphisms. A strong association of class I allele B*15:02 was specified. For this reason, genotyping is now done in Asian ethnic groups before starting treatment with said medication [103].

Despite the above, more information must be available for personalized therapy against autoimmune diseases and HSR. The cumulative knowledge of physiopathology, their better-defined classifications, and the identification of autoantigens, together with their corresponding antibodies, lead to the generation of increasingly safe and effective therapeutic strategies [93, 104].

5.2 Neurological diseases

They affect the body's autonomic, peripheral, and central nervous systems. The most common are epilepsy, Alzheimer's, and Parkinson's. However, others, such as migraines, can be located within this area [105]. According to data from the World Health Organization (WHO) for 2019, Alzheimer's and other dementias were the second cause of death for high-income nations, responsible for 814,000 deaths [106].

On the other part, according to the Centers for Disease Control and Prevention (CDC), in 2021, 119,399 deaths from Alzheimer's were reported in the United States [107]. Regarding the American region, the Pan American Health Organization (PAHO) reported 533,172 deaths from neurological disorders throughout 2019 [105].

Epilepsy is characterized by recurrent and unpredictable interruptions of normal brain function called epileptic seizures. Brain dysfunction may result from distinct causes [108].

Genetic polymorphisms present in phase I biotransformation enzymes, specifically CYP2C9, CYP2C19, and CYP3A4/3A5, and phase II (uridine diphosphate glucuronyltransferase or UDP-UGT), are of clinical relevance for its treatment. Phenytoin, one of the primary drugs available for epileptic seizures, is metabolized mainly by CYP2C9 (about 90 %) and a little by CYP2C19. If there is function loss in some variants of the alleles that encode for these enzymes, there is an elimination decrease, with the consequent rise in blood and a greater neurotoxicity risk. More than 50 variants have been identified in the gene that encodes for CYP2C9, confirming its high polymorphism [44, 109]. Hence, their role is to identify necessary adaptations regarding their employment.

As a complement, in an observational study with 23 drug-resistant epilepsy patients, a genomic DNA analysis was performed. It was identified that the relevant SNPs were CYP2D6*2, CYP2D6*4, CYP2C19*2, and CYP3A4*1B, which were related to poor metabolizers. These variations can affect the response to antiepileptic drugs and generate therapy resistance [110].

In another study involving 98 children with epilepsy in China, a relationship was found between the valproic acid plasma concentration and SNPs involving UDP-UGT, specifically UGT1A6 and UGT2B7, and CYP2C9. Individuals with specific polymorphisms in UGT1A6 exhibited lower plasma concentrations and required higher doses. In this way, these mutations affect the metabolism of said substance in epileptic people [111].

On the other hand, Alzheimer's is the most common neurodegenerative disorder and the most common cause of dementia, accounting for approximately half of all cases. The prevalence is approximately 30 % among people 85 years

and older. Its primary clinical manifestation is accelerated cognitive function loss. Alterations in mood and behavior are seen, followed by memory loss, disorientation, and aphasia. The hippocampus and cerebral cortex are the most frequently affected areas [112].

Besides, senile plaques and neurofibrillary tangles are characteristic lesions in affected tissues. Senile plaques in hippocampal blood vessels and neurons mainly comprise --β. The protein is produced due to a proteolytic process mediated by α, β, and γ secretases, which break down the amyloid precursor protein (APP) and divide it into components, including amyloid-β [113, 114].

The tangles are filamentous bundles of abnormal tau proteins, which accumulate in the cytoplasm of affected neurons. These macromolecules mainly promote and maintain the structure of microtubules through the C-terminal domain union. Both amyloid-β and tau proteins form insoluble clumps widely associated with this illness [113, 114].

This health problem has an autosomal dominant inheritance pattern. Three mutations in genes that code for proteins involved in amyloid plaque formation (APP, presenilin-1, and presenilin-2) cause early-onset Alzheimer's. A non-familial condition has been associated with the apolipoprotein E ε4 allele (ApoE-ε4) gene. A very low-density lipoprotein transporter gene is required for amyloid-β deposition [112, 115].

In a meta-analysis with 1266 patients with Alzheimer's who were treated with donepezil, polymorphisms in CYP2D6 or ApoE were associated with the effectiveness of treatment. A significant descent in the drug response was achieved for those with variations in both genes [116].

Another study analyzed DNA from the brain region of 71 individuals with the pathology and 81 controls. Variants were searched for different amyloid-β transporters, specifically ABCA1, ABCA7, ABCB1, ABCC2, and ABCG2, some of which were related to the Apoε4 presence or absence. It was found that an ABCA7 polymorphism is related to the disorder and that ABCB1 is involved in the amyloid-β accumulation process in the brain [117].

Parkinson's (second most common neurodegenerative) is a movement condition whose main clinical characteristics are substantial movement absence, tremors at rest, rigidity, bradykinesia, and postural instability. The cause behind this is a loss of dopamine-producing neurons in the midbrain substantia nigra [112, 118]. Additionally, processes such as altered mitochondrial function and dopamine metabolism, oxidative stress, abnormal protein aggregation, inflammation, necrosis, and accelerated apoptosis are presented. Intracellular deposits of α-synuclein, ubiquitin, and other protein aggregates (Lewy bodies) have also been discovered in many neurons and are medical features [112].

The gene that encodes the α-synuclein protein and alterations in dopamine receptors are involved in its early and rapid onset. Likewise, mutations in leucine-rich repeat kinase 2 (LRRK2 or PARK8 gene), parkin-2 (PARK2), and PTEN-induced kinase I (PINK1 or PARK6) have been associated with late-onset, contributing to the augmented risk of illness developing [112, 115, 119].

A study with 199 patients who received levodopa assessed the relationship between dyskinesia and polymorphisms in the DRD2/ANKK1 dopamine receptor gene. The results showed that its variants influence the induction of involuntary movements (dyskinesia) in drug administration [120].

In another study of 228 patients with idiopathic Parkinson's, polymorphisms in the regions for DRD1 and DRD3 were analyzed. A possible relationship between genetic variants and motor complications due to levodopa use was analyzed. It was concluded that a particular polymorphism (DRD1 A48G) may influence dyskinesia [121].

5.3 Cardiovascular pathologies

Cardiovascular events are one of the leading causes of morbidity and mortality worldwide. According to the WHO, around 18 million lives are lost yearly. Even a third of these deaths occur in people under 70 years of age, which is alarming [122].

Another associated problem is that drugs, such as anticoagulants and antiarrhythmics, intended for its treatment have shown highly variable metabolic response ranges because of patients' genetic characteristics. This problem exemplifies the need to find instruments to define adequate doses to maximize drug therapy sensitivity and specificity [123].

Pharmacogenomic studies have focused on existing and commonly employed pharmaceutical products at the clinical level. Guidelines have even been created with therapeutic dosage recommendations based on the genotype of the biomarkers. One of the most studied has been warfarin. It is administered orally as a racemic mixture of S- and R-warfarin

and is indicated to prevent and treat thromboembolic events. Its mechanism of action is based on the VKOR enzyme inhibition, which leads to vitamin K depletion in its reduced form and the synthesis inhibition of the coagulation factors II, VII, IX, and X, and the anticoagulant proteins S and C. The result is a decrease in prothrombin levels and the consequent reduction in the blood clots' thrombogenicity [123, 124, 125].

The interindividual variability of its response has been associated with SNPs, mainly those of the CYP450 family, like CYP2C9, which participates in metabolizing its S enantiomer [123, 124]. The polymorphisms related to these metabolic enzymes promote varied catalytic activity. The allele with total enzymatic activity has been designated CYP2C9*1, and its allelic variants are CYP2C9*2 and CYP2C9*3. They present the arginine change for cysteine at position 144 of the protein (Arg144Cys) and isoleucine for leucine at position 359 (Ile359Leu), respectively. They are the most common in world populations. Thanks to pharmacogenomic studies, it has been established that the *2 allele is linked with a 30 % decrease in enzyme activity. In comparison, the *3 allele is correlated with a reduction of up to 95 % in warfarin metabolism compared to that of CYP2C9*1. Therefore, it is mandatory to make dose adjustments according to the person's metabolizing condition [123, 124, 126].

Furthermore, VKOR can be mentioned as part of drug metabolism pathways. It is characterized by a vital polymorphism (VKORC1) linked with changes regarding the metabolizing phenotype of individuals against said drug [124, 127].

A study evaluated the effects of the presence of CYP2C9 and VKORC1 polymorphisms regarding the cardiovascular patients' sensitivity towards warfarin and the response capacity. Both variables were analyzed during the treatment stabilization phase. Three CYP2C9 and four VKORC1 polymorphisms were studied. The work helped determine that persons with more than one VKORC1 variant were at augmented risk of warfarin sensitivity (excessive anticoagulation) compared to those with one or no polymorphisms. This result was similar to those with more than one CYP2C9 polymorph. They exhibited a higher sensitivity risk to the molecule than persons with one or no polymorphs [124].

Another interesting detail was that volunteers with a single CYP2C9 or VKORC1 polymorph required significantly lower doses than patients without such variants. In summary, the presence of polymorphisms is associated with increased sensitivity to warfarin during therapeutic stabilization [124].

The FDA currently recommends that genetic modifications related to CYP2C9 and VKORC1 be determined before warfarin treatment starts to adjust the dose correctly. Pharmacogenomics' importance is evident in generating more effective and safer therapies and solving patients' problems regarding an adequate response through a suitable and supported dose adjustment [123, 128, 129].

Likewise, clopidogrel belongs to the ticlopidine family and has antiplatelet action. It is indicated for inhibiting blood clot synthesis at the peripheral, coronary, or cerebral arteries. Also, it is a standard treatment for acute coronary syndrome, acute myocardial infarction, and cerebrovascular attacks. It must first be transformed into the active metabolite to exert its therapeutic effect, corresponding to about 5 % of the prodrug. Numerous enzymes, including CYP2C19, mediate this transformation. This metabolite inhibits the adenosine diphosphate receptor P2Y12, expressed on platelets [123, 130, 131].

Through studies, it has been possible to establish polymorphs responsible for interindividual differences. It is estimated that 30 allelic gene variations are responsible for protein synthesis. Some of the most common are CYP2C19*2, CYP2C19*3, CYP2C19*4, and CYP2C19*17 [123, 131, 132].

With CYP2C19*2, a decrease in the metabolite in blood has been reported, reducing antiplatelet activity and promoting the risk of cardiovascular accidents [123]. Besides, CYP2C19*2, CYP2C19*2, and CYP2C19*4 characterize intermediate and poor metabolizers, while CYP2C19*17 carriers are classified as extensive metabolizers [132].

Biochemical drug monitoring tests, such as measuring serum prothrombin concentration or platelet aggregometry tests, are routinely executed. These assays only show the response to the indicated dose but do not function to predict the reaction of a specific patient prior to the treatment beginning, as pharmacogenomic assays can do [123]. Through them, it is possible to find gene polymorphs dependable for the pharmacological action associated with the medication [133].

5.4 Oncology

Cancer involves a complex carcinogenesis process that encompasses genetic and epigenetic factors [49]. Historically, it has been one of the leading death causes. In 2020, there were nearly 10 million fatalities [134]. However, mortality has declined in recent decades thanks to reduced smoking, early diagnosis, minimization of toxicities, and improved treatments through specific biomarkers [135].

Pharmacogenomics is leading in this area, with implications for therapeutic selection, treatment, dosing, and risk prediction [39]. For clinical decision-making, a better understanding of how drugs and adjuvant agents used for this pathology are metabolized is essential [136].

One of the therapies is chemotherapy. It is highly toxic and is usually administered in high doses. The combination of chemotherapeutic agents provokes side effects in 50 % of individuals. In addition, they have a narrow therapeutic index, challenging the management of toxicities [137]. Serious side effects include myelosuppression, renal failure, elevated transaminases, heart failure, tumor lysis syndrome, diarrhea, thrombosis, pulmonary fibrosis, secondary tumors, constipation, pneumonitis, and seizures [135].

Thiopurine S-methyltransferase (TPMT) is a relevant biomarker responsible for 6-mercaptopurine inactivation, an FDA-approved chemotherapeutic to treat leukemia [137]. It inhibits purine synthesis and acts as an antiproliferative agent, interfering with the synthesis of proteins, DNA, and RNA and promoting proliferative T lymphocyte apoptosis [138].

TPMT polymorphisms vary up to ten times the steady-state concentration in patients with the same dose. Those with elevated 6-MP concentrations may induce severe myelosuppression [136]. Treatment in children with acute lymphocytic leukemia depends on the maximum tolerable drug dose [139].

Slow metabolizers can tolerate the full dose for only 7 % of the total treatment time, while intermediate or normal metabolizers do so for 65 and 84 %, respectively. For this reason, the Clinical Pharmacogenetics Implementation Consortium (CIPC) formulated a guideline recommending the usual dose for normal metabolizers, a 30 to 70 % reduction for intermediate metabolizers, and a 90 % reduction for poor metabolizers [139].

Breast cancer is the most common in women and ranks second in mortality. The therapeutic options are surgery, chemotherapy, radiotherapy, and hormonal therapy [140]. The presence of hormone receptors is a determining factor in choosing a therapeutic regimen. Generally, estrogen receptors are expressed in most tumors. Several studies have demonstrated the usefulness of selective modulators of such receptors, such as tamoxifen, as an effective therapy and preventive agent against tumor recurrence [141].

Tamoxifen is the preferred drug for treating estrogen receptor α-positive premenopausal patients [142]. It is a selective estrogen receptor modulator. Its anti-estrogenic effect blocks the hormone action, which stimulates the development of the tumor cells by competing for binding to the estrogen receptor α [142, 143]. The substance requires metabolic activation by the CYP2D6 enzyme, generating the active metabolites 4-hydroxyitamoxifen and endoxifen, managers of therapeutic effects [141]. CYP2D6 alleles can confer normal, decreased, or no activity and cause a wide activity range among the population. Such variations are associated with reduced endoxifen metabolite concentration, the product of an enzyme-reduced activity [140].

To relate the predicted CYP2D6 phenotype and serum endoxifen concentrations with disease-free survival, a multicenter trial was performed in patients with early breast cancer who received adjuvant tamoxifen. Individuals were genotyped for genetic variants in the CYP2D6 gene and classified as ultrarapid, extensive, intermediate, and poor metabolizers. Through a dose escalation of tamoxifen, there was a significant increase in serum concentrations in poor and intermediate metabolizers. In the case of the slow ones, the endoxifen mean level augmented from 24 to 81 % compared to the mean concentration in extensive metabolizers [144].

For its part, 5-fluorouracil (5-FU) is a prevalent and effective chemotherapeutic agent for treating head and neck, breast, pancreas, and gastrointestinal tract cancer [145]. Furthermore, it is prescribed for advanced colon cancer in adjuvant chemotherapy [146]. Its cytotoxicity mechanism has been attributed to misincorporating its metabolites into RNA and DNA and the thymidylate synthase (TS) enzyme inhibition [145]. This molecule catalyzes the deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP) conversion, one of the nucleotides that form thymine [147]. By its inhibition, there is a drop in DNA replication and repair, with the consequent arrest of tumor cell growth [146]. The most common adverse effects comprise dose-dependent hematologic and gastrointestinal toxicities and skin reactions like hand-foot syndrome [148].

Another important enzyme is dihydropyrimidine dehydrogenase (DPD). Individuals with diminished activity are at high risk of supratherapeutic concentrations with standard dosing since the drug half-life is increased. This situation can lead to severe toxicity [145, 148]. DPD activity is highly heterogeneous in the population, partly attributable to its encoding gene CPYD variability [148].

Given the above, the Netherlands National guideline for colorectal carcinoma recommends DPD testing before therapy to optimize efficacy and avoid side effects [149]. Additionally, two guidelines have been created to help clinicians interpret

DPYD genotypes and adjust the 5-FU dose published by CPIC and the Dutch Pharmacogenetics Working Group (DPWG) [148, 150, 151].

Finally, when put into clinical practice in a schematic and orderly manner, pharmacogenomics represents a central opportunity for advancement in the medical area to improve the health conditions of the entire population. The value given to this branch is reflected in the COVID-19 pandemic. Options have been sought to enhance treatments, elucidating markers and genetic variants of interest in treatments with chloroquine and hydroxychloroquine [152] and other medications considered for this infection [153, 154, 155].

6. CONCLUSIONS

Research on the relationships between genomic sciences and pharmacological therapy led to the birth of pharmacogenomics as a pharmaceutical science. Its implementation allows individualizing drug selection and administration to avoid adverse consequences and maximize effectiveness.

This knowledge has a wide range of purposes. Nonetheless, it is necessary to understand better aspects related to interindividual variability, pharmacodynamics, pharmacokinetics, and biomarkers associated with pharmacological treatments.

There are different pathologies where this knowledge has been put into practice, including immunological, neurological, and cardiovascular diseases and cancer. Therefore, it is inevitable that its utilization will increase in the short and medium term, for which the work of each nation's health authorities is indispensable, who would oversee assessing its advantages and disadvantages, always putting the patients' quality of life first.

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