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Pharmacogenomics: Generalities and Applications in the Pharmaceutical Sciences

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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

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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 prioritizing the patient's quality of life.

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 (Herrero Sáenz, 2019). 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 (De Anca Escudero, 2009). 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 (Valenzuela, 2020).

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 (Gil del Valle et al., 2017). Some products where this phenomenon is observed are:

- **Warfarin**: a polymorphism in the cytochrome P450 2C9 (CYP2C9) gene participates in its metabolism and the S-enantiomer inactivation (Vélez Gómez et al., 2018).
- **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 (Brewster and Seedat, 2013).

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 (Weinshilboum and Wang, 2017), based on identifying genetic variants that influence its pharmacokinetics and pharmacodynamics (Kaye et al., 2018). 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 (Cacabelos et al., 2019).

Pharmacogenomics has become an essential component of personalized medicine (Dunnenberger et al., 2016), 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 (Di Sanzo et al., 2017). Additionally, it ponders the environment and lifestyle to determine the best way to prevent or treat the condition (Sisodiya, 2021).

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 (Ortiz and Tabak, 2012). Such mutations are genetic deoxyribonucleic acid (DNA) variants in more than 1 % of the world population (Rosero et al., 2017).

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) (Ortiz and Tabak, 2012; Tafur-Betancourt et al., 2017). Therefore, the principal objective of pharmacogenomics is to predict an individualized drug treatment based on each

person's genetic profile obtained through a genome study (Rodríguez Duque and Miguel Soca, 2020).

Likewise, it is necessary to distinguish between pharmacogenetics and pharmacogenomics. The first refers to interindividual variability under the influence of genetic factors. 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 (Prior-González et al., 2011).

The historical pharmacogenomics bases arise from James Watson and Francis Crick's elucidation of DNA structure in the 1950s (Watson and Crick, 1953). 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 (Daudén Tello, 2006).

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 (Frigolet and Gutiérrez-Aguilar, 2017).

Metabolomics analyzes the concentration changes of specific metabolites according to the body's responses to genetic variation. It also permits obtaining a sample metabolic profile, both qualitatively and quantitatively (Frigolet and Gutiérrez-Aguilar, 2017).

Finally, genomics is dedicated to investigating the complete genome. It allows studies of gene identification, characterization, interaction, and function (Frigolet and Gutiérrez-Aguilar, 2017).

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 (Daudén Tello, 2006).

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 (Pierna Álvarez et al., 2019).

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 (Landouré et al., 2012).

Furthermore, genome-wide association studies have identified genetic variations that impact 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 (Sud et al., 2017).

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 (Quiñones et al., 2017; Rodríguez Duque and Miguel Soca, 2020). Researchers aim to find biomarkers associated with the diagnosis, prognosis, and treatment response (Quiñones et al., 2017).

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 (Li et al., 2009). 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 (Li et al., 2009; Relling and Evans, 2015).

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) (Fan et al., 2017).

Variation in HLA genes defines susceptibility to autoimmune diseases, infections, and immune reactions (Fan et al., 2017). HLA-B*57:01 gene carriers have a high-risk factor for hypersensitivity to abacavir (Quiñones et al., 2017; Relling and Evans, 2015; Rodríguez Carranza, 2013). 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 (Rodríguez Carranza, 2013). Its administration in this group can trigger Stevens-Johnson syndrome (SJS) and toxic epidural necrolysis (TEN) (Wake et al., 2022).

Both are hypersensitivity reactions (HSRs), 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 (Dispenza, 2019; Vyas et al., 2023), as shown in Table 1.

SJS and TEN are considered type 4 HSRs 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 % (Charlton et al., 2020; Dodiuk-Gad et al., 2015; Lerch et al., 2018).

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 (Roden et al., 2019).

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 effect (Fricke-Galindo et al., 2018).

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 (Klein et al., 2017; Smith et al., 2016). The FDA changed the drug's label, incorporating information on allele genomics as a marker, and recommended genotyping in this population (Klein et al., 2017).

Table 1. Types of hypersensitivities and their main characteristics (Dispenza, 2019; Vyas et al., 2023)

Hypersensitivity type	Characteristics
Type 1 HSR	-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 HSR	-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 HSR	-IgM and IgG antibodies bind to the antigen, forming immune complexes. -The complexes are deposited in various tissues, causing an inflammatory reaction.
Type 4 HSR	-Delayed type reactions are observed (the response is reflected 48 to 72 hours after the immune reaction). -They are mediated by T cells.

In transplant patient care, polymorphisms in the ABCB1, CYP3A4, and CYP3A5 genes are recognized and considered to optimize tacrolimus therapy (García-González et al., 2016). This therapeutic option has favored patient survival after transplant. 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 (Provenzani et al., 2013). Its indication has spread as a first-line option for intestine, kidney, heart, lung, and bone marrow transplants (Yu et al., 2018) since adequate immunosuppressive therapy is essential to maintain high allograft viability and prevent acute rejection (García-González et al., 2016). Nevertheless, genetic factors influence absorption, metabolism, excretion, and drug response (Yu et al., 2018).

Because of these findings, the FDA recognized that pharmacogenomics plays a critical role. Now, pharmaceutical products can contain information on genetic biomarkers (García-González et al., 2016). Labeling aims to inform patients and health personnel on the proper use of the product and facilitate its understanding. It is a tool in health education and is referenced every day in practice by health professionals (Ramírez-Telles and Argotti-Rodríguez, 2022).

An extensive list of therapeutic medications with pharmacogenomic information on their respective biomarkers has been created (U.S. Food & Drug Administration, 2024). Thus, this science has found an application field in therapeutic areas such as psychiatry (Quiñones et al., 2017; Rodríguez Duque and Miguel Soca, 2020), analgesia (Quiñones et al., 2017), neurology (Balestrini and Sisodiya, 2018; Carr et al., 2021; Gilman et al., 2014; Quiñones et al., 2017; Rodríguez Duque and Miguel Soca, 2020), oncology (Carr et al., 2021; Rodríguez Duque and Miguel Soca, 2020), and cardiology (Rodríguez Duque and Miguel Soca, 2020; Quiñones et al., 2017; Scibona et al., 2014).

4. FACTORS AFFECTING PHARMACO-GENOMICS

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 (Quiñones et al., 2017).

According to the above, there are factors related to the drug. Some are physicochemical characteristics, administration routes, dosage, excipients, and interactions with other medicines (Quiñones et al., 2017; Turner et al., 2015).

Concerning genetic factors, metabolic enzymatic activity, transporters' efficiency, and some receptors' sensitivity must be considered (Lewis et al., 2017; Quiñones et al., 2017; Soni et al., 2020). The interindividual variability in the expression of the genes of drug-metabolizing enzymes such as CYPs and some transporters is more remarkable than other types (Yang et al., 2013).

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 (Alvarado-González and Arce Jiménez, 2013).

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 (Swathy and Banerjee, 2022). 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 (Ahmed et al., 2020).

Likewise, environmental aspects, comprising smoking, alcohol consumption, and diet, affect the differentiated response between patients (Quiñones et al., 2017).

Finally, the elements of the person must be pondered. They incorporate age, sex, pregnancy, lactation, renal and hepatic functions, and pathologies (Quiñones et al., 2017). 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 (Trenaman et al., 2021). Together, these characteristics significantly vary the pharmaceutical product response.

4.2 Pharmacokinetics and Pharmaco-dynamic Variability

The genetic variability of populations and individuals significantly affects other pharmaceutical processes in the human body, such as pharmacokinetics and pharmacodynamics (Guio et al., 2015). These sciences oversee studying the interactions and mechanisms of action of drugs within the organism (Llerena, 2021). Regarding pharmacokinetics, the variability of the drug absorption, distribution, metabolism, and excretion (ADME) processes is being investigated (Doogue and Polasek, 2013).

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 (Arrieta-Bolaños et al., 2012; Llerena, 2021).

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. 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 (Llerena, 2021; Moore et al., 2021). 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 (Llerena, 2021; Valenzuela Jiménez et al., 2013).

Pharmacogenomics aims to create a relationship with pharmacokinetics for drug dosage personalization. This synergy seeks to improve its benefits and reduce consumption risks (Moore et al., 2021).

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 blood concentration have been identified (Belmonte Campillo, 2018), as seen in Table 2. This classification has helped to identify people who suffer from substance poisoning, even when administered at regular doses (Schulz et al., 2012).

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 (Belmonte Campillo, 2018; Ortiz and Tabak, 2012).

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 (Rodríguez Duque and Miguel Soca, 2020).

Genetic variation is provoked by structural differences in particular genes or variations in portions with regulatory activity (insertions, deletions, duplications, inversions, or substitutions of nitrogenous bases modifying the DNA sequence). This situation generates a change in gene functionality, which results in the synthesis of modified proteins (Betcher and George, 2020).

Table 2. Definition of drug metabolic phenotypes (Belmonte Campillo, 2018; National Human Genome Research Institute, 2024)

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 by drug accumulation.

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 (Ferrer et al., 2009).

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 (Ferrer et al., 2009).

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) (Betcher and George, 2020; Hosseini et al., 2022)

SNPs occur when a paired base pair is substituted within the nucleotide sequence. The variation in a regulatory area or gene can alter the encoded protein synthesis (Betcher and George, 2020).

For its part, CNVs occur 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 (Orrico, 2019).

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 (Aguirre Fernández et al., 2017; Alshabeeb et al., 2019; Díaz Fernández and Rodríguez Ferreiro, 2016; Litman, 2019). Table 3 lists some of those studied together with drugs associated with each other and the clinical area where these medications are used.

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 (Hikino et al., 2018; Vivot et al., 2015). Some of these areas are explained in more detail.

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

Biomarker	Drug	Therapeutic area
CYP2C19	Formoterol (Martinez-Matilla et al., 2019)	Pulmonary
	Carisoprodol (Pratt et al., 2018)	Rheumatology
	Citalopram (Pratt et al., 2018)	Psychiatry
	Clopidogrel (Pratt et al., 2018)	Cardiology
	Diazepam (Pratt et al., 2018)	Neurology
	Voriconazole (Pratt et al., 2018)	Infectious diseases
CYP2C9	Celecoxib (Siu et al., 2018)	Rheumatology
	Meloxicam (Cottrill et al., 2021)	Anesthesiology
	Phenytoin (Cottrill et al., 2021)	Neurology
	Piroxicam (Cottrill et al., 2021)	Rheumatology
	Warfarin (Kaye et al., 2020)	Hematology
CYP2D6	Tamoxifen (Kiyotani et al., 2012)	Oncology
	Venlafaxine (Ahmed et al., 2019)	Psychiatry
	Tramadol (Zhu et al., 2021)	Anesthesiology
	Propranolol (Geng et al., 2021)	Cardiology
TPMT	Azathioprine (Taha et al., 2021)	Rheumatology
	Cisplatin (Olgun et al., 2016)	Oncology
	Mercaptopurine (Strohbuscha and Kator, 2020)	Oncology
	Tioguanine (Strohbuscha and Kator, 2020)	Oncology
VKORC1	Warfarin (Kaye et al., 2020)	Hematology
CYP1A2	Rucaparib (Konecny et al., 2021)	Oncology
UGT1A6	Valproic acid (Mani et al., 2021)	Neurology
EGFR	Cetuximab (Hirsch et al., 2022)	Oncology
HER2	Trastuzumab (Hertz et al., 2009)	Oncology
HLA-B	Carbamazepine (Min et al., 2022)	Neurology

5.1 Immunological Disorders

HSRs and autoimmune problems affect a significant percentage of the world 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 (Mainet-González, 2018).

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 (Tavakolpour et al., 2018). For example, glucocorticoids can provoke Cushing's syndrome by increasing cortisol in the blood. Its manifestations comprise edema, weight gain, and striae (Lima-Martínez et al., 2013).

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 (Wraith, 2016).

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 (Moote et al., 2018).

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 (Richardson et al., 2020).

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 (Mainet-González, 2018).

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 (Tavakolpour et al., 2018).

Therefore, pharmacogenomics locates genetic determinants involved with the efficacy or toxicity of the therapeutic options available against these conditions, finding the best therapeutic route. 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 ATP binding cassette (ATP) transporters, and pharmacodynamics, specifically the Fc gamma receptor (FcγR) and toll-like receptors (TLR) (Barliana et al., 2022).

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 (Barliana et al., 2022).

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 (Tavakolpour et al., 2018). 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 (Walczak et al., 2020).

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. These polymorphisms prevent the blockade of the interaction between TNF-α and the binding sites of its cell surface receptors (p55 and p75) (Puentes Osorio et al., 2018).

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 (Khan and Phillips, 2020). Even associations with HLA-encoded MHC genes have been accomplished (Sukasem et al., 2014).

Candidate gene and genome-wide association studies have been valuable in identifying elements related to allergic reactions' susceptibility to various medications. The HLA genes encode proteins associated with antigen presentation to T cells, which may be predictors of HSRs. 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 (Daly, 2013).

Despite the above, more information must be available for personalized therapy against autoimmune diseases and HSRs. 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 (Arbitrio et al., 2021; Tavakolpour et al., 2018).

5.2 Neurological Diseases

They affect the body's autonomic, peripheral, and central nervous systems. The most common are epilepsy, Alzheimer's disease, and Parkinson's disease. However, others, such as migraines, can be located within this area (Pan American Health Organization, 2021). According to data from the World Health Organization (WHO) for 2019, Alzheimer's disease and other dementias were the second cause of death in high-income nations, responsible for 814,000 deaths (World Health Organization, 2024b).

On the other part, according to the Centers for Disease Control and Prevention (CDC), in 2021, 119,399 deaths from Alzheimer's disease were reported in the United States (National Center of Health Statistics, 2020). Regarding the American region, the Pan American Health Organization (PAHO) reported 533,172 deaths from neurological disorders throughout 2019 (Pan American Health Organization, 2021).

Epilepsy is characterized by recurrent and unpredictable interruptions of normal brain function called epileptic seizures. Brain dysfunction may result from distinct causes (Fisher et al., 2005).

Genetic polymorphisms present in phase I biotransformation enzymes, specifically CYP2C9, CYP2C19, and CYP3A4/3A5, and phase II biotransformation enzymes (uridine diphosphate glucuronyl transferase 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 (Balestrini and Sisodiya, 2018; Božina et al., 2019). Hence, the role of pharmacogenomics is to identify necessary adaptations for 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 (López-García et al., 2017).

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. 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 (Guo et al., 2012).

On the other hand, Alzheimer's disease 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 (Checkoway et al., 2011).

Besides, senile plaques and neurofibrillary tangles are characteristic lesions in affected tissues. Senile plaques in hippocampal blood vessels and neurons mainly comprise amyloid-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 (Carvajal Carvajal, 2016; López-Camacho et al., 2017).

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 (Carvajal Carvajal, 2016; López-Camacho et al., 2017).

This health problem has an autosomal dominant inheritance pattern. Three gene mutations that encode proteins involved in amyloid plaque formation (APP, presenilin-1, and presenilin-2) cause early-onset Alzheimer's disease. A non-familial condition has been associated with the apolipoprotein E (ApoE) allele gene. A very low-density lipoprotein transporter gene is required for amyloid-β deposition (Cacabelos, 2020; Checkoway et al., 2011).

In a meta-analysis with 1266 patients with Alzheimer's disease who were treated with donepezil, polymorphisms in CYP2D6 or ApoE were associated with the treatment effectiveness. A significant descent in the drug response was achieved for those with variations in both genes (Xiao et al., 2016).

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 ApoE4 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 (Cascorbi et al., 2013).

Parkinson's disease (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 source behind this is a loss of dopamine-producing neurons in the midbrain substantia nigra (Checkoway et al., 2011; Hurtado et al., 2016). 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 (Checkoway et al., 2011).

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 (Cacabelos, 2020; Checkoway et al., 2011; Payami, 2017).

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 (Rieck et al., 2012).

In another study of 228 patients with idiopathic Parkinson's disease, polymorphisms in the regions for DRD1 and DRD3 were analyzed. The study analyzed a possible relationship between genetic variants and motor complications due to levodopa use. It concluded that a particular polymorphism (DRD1 A48G) may influence dyskinesia (Dos Santos et al., 2019).

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 (World Health Organization, 2024a).

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 (Vélez Gómez et al., 2018).

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 (Al-Eitan et al., 2019; Pratt et al., 2020; Vélez Gómez et al., 2018).

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 (Al-Eitan et al., 2019; Vélez Gómez et al., 2018). 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 (Al-Eitan et al., 2019; Kuzikov et al., 2022; Vélez Gómez et al., 2018).

Furthermore, VKOR can be mentioned as part of drug metabolism pathways. It is characterized by

a vital polymorphism (VKORC1) linked with changes in individuals' metabolizing phenotype against said drug (Al-Eitan et al., 2019; Li et al., 2020).

A study evaluated the effects of CYP2C9 and VKORC1 polymorphisms regarding cardiovascular patients' sensitivity toward warfarin and their 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 variant. They exhibited a higher sensitivity risk to the molecule than persons with one or no polymorphism (Al-Eitan et al., 2019).

Another interesting detail was that volunteers with a single CYP2C9 or VKORC1 polymorphism 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 (Al-Eitan et al., 2019).

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 (Al-Saikhan, 2020; Vélez Gómez et al., 2018; Zhu et al., 2020).

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 (Kuo et al., 2022; Kuszynski et al., 2021; Vélez Gómez et al., 2018).

Studies have made it possible to establish polymorphisms 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 (Kuo et al., 2022; Montazid et al., 2021; Vélez Gómez et al., 2018).

CYP2C19*2 has been reported to decrease the metabolite in blood, reduce antiplatelet activity, and promote the risk of cardiovascular accidents (Vélez Gómez et al., 2018). CYP2C19*2, CYP2C19*3, and CYP2C19*4 characterize intermediate and poor metabolizers, while CYP2C19*17 carriers are classified as extensive metabolizers (Montazid et al., 2021).

Biochemical drug monitoring tests, such as serum prothrombin concentration or platelet aggregometry tests, 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 (Vélez Gómez et al., 2018). Through them, it is possible to find gene polymorphisms dependable for the pharmacological action associated with the medication (Pratt et al., 2021).

5.4 Oncology

Cancer involves a complex carcinogenesis process that encompasses genetic and epigenetic factors (Soni et al., 2020). Historically, it has been one of the leading death causes. In 2020, there were nearly 10 million fatalities (Sung et al., 2021). However, mortality has declined in recent decades thanks to reduced smoking, early diagnosis, minimization of toxicities, and improved treatments through specific biomarkers (Zhang et al., 2016).

Pharmacogenomics is leading in this area, with implications for therapeutic selection, treatment, dosing, and risk prediction (García-González et al., 2016). For clinical decision-making, a better understanding of how drugs and adjuvant agents used for this pathology are metabolized is essential (Patel et al., 2021).

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 (Elzagallaai et al., 2021). Serious adverse effects include myelosuppression, renal failure, elevated

transaminases, heart failure, tumor lysis syndrome, diarrhea, thrombosis, pulmonary fibrosis, secondary tumors, constipation, pneumonitis, and seizures (Zhang et al., 2016).

Thiopurine S-methyltransferase (TPMT) is a relevant biomarker responsible for 6-mercaptopurine inactivation, an FDA-approved chemotherapeutic to treat leukemia (Elzagallaai et al., 2021). 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 (Fernández-Ramos et al., 2017).

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 (Patel et al., 2021). Treatment in children with acute lymphocytic leukemia depends on the maximum tolerable drug dose (Mlakar et al., 2016).

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 (Mlakar et al., 2016).

Breast cancer is the most common in women and ranks second in mortality. The therapeutic options are surgery, chemotherapy, radiotherapy, and hormonal therapy (Reis et al., 2019). The presence of hormone receptors is a determining factor in choosing a therapeutic regimen. Generally, estrogen receptors are expressed in most tumors. Several investigations have demonstrated the usefulness of selective modulators of such receptors, such as tamoxifen, as an effective therapy and preventive agent against tumor recurrence (Chan et al., 2020).

Tamoxifen is the preferred drug for treating estrogen receptor α-positive premenopausal patients (Cronin-Fenton and Damkier, 2018). 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 (Ariza Márquez et al., 2016; Cronin-Fenton and Damkier, 2018). The substance requires metabolic activation by the CYP2D6 enzyme, generating the active metabolites 4-hydroxyitamoxifen and endoxifen, managers of therapeutic effects (Chan et al., 2020). 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 (Reis et al., 2019).

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 (Dezentjé et al., 2015).

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 (Matsusaka and Lenz, 2015). Furthermore, it is prescribed for advanced colon cancer in adjuvant chemotherapy (Xie et al., 2020). Its cytotoxicity mechanism has been attributed to misincorporating its metabolites into RNA and DNA and the thymidylate synthase (TS) enzyme inhibition (Matsusaka and Lenz, 2015). This molecule catalyzes the deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP) conversion, one of the nucleotides that form thymine (Nelson et al., 2016). By its inhibition, there is a drop in DNA replication and repair, with the consequent arrest of tumor cell growth (Xie et al., 2020). The most common adverse effects comprise dose-dependent hematologic and gastrointestinal toxicities and skin reactions like hand-foot syndrome (Hamzic et al., 2020).

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 augmented. This situation can lead to severe toxicity (Hamzic et al., 2020; Matsusaka and Lenz, 2015). DPD

activity is highly heterogeneous in the population, partly attributable to its encoding gene CPYD variability (Hamzic et al., 2020).

Given the above, the Netherlands National guideline for colorectal carcinoma recommends DPD testing before therapy to optimize efficacy and avoid side effects (Martens et al., 2020). Additionally, two guidelines published by CPIC and the Dutch Pharmacogenetics Working Group (DPWG) have been created to help clinicians interpret DPYD genotypes and adjust the 5-FU dose (Amstutz et al., 2018; Hamzic et al., 2020, Lunenburg et al., 2020).

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 (Babayeva and Loewy, 2020) and other medications considered for this infection (Al-Taie et al., 2022; Badary, 2021; Stevenson et al., 2021).

This knowledge has also been employed in veterinary clinical practice. The studies had been done on animals such as cats, dogs, and cattle (Vaidhya et al., 2024).

6. CONCLUSION

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 prioritizing the patient's quality of life.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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