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Pharmacogenomics: Basis and Milestones

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Synonyms

Cytochrome P450 (CYP); Cytochrome P450 isozymes; Cytochrome P450 monooxygenases; Genetic variant; Mixed-function oxidases; Personalized medicine; Polymorphism; Precision medicine

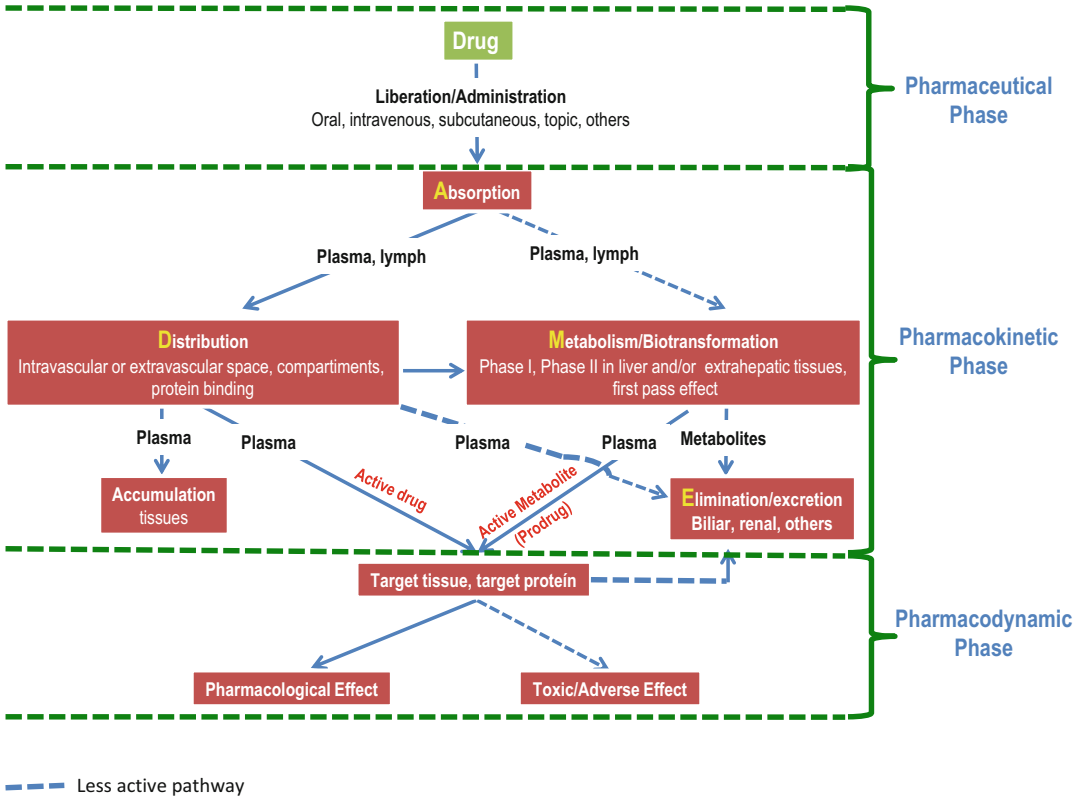
Definition

The genomic interindividual heterogeneity for proper pharmacotherapy remains a significant challenge for research, clinical decision-making, and the design of clinical trials. Translation of the obtained genomic information into actionable clinical advice lags behind, mainly due to insufficient powered and representative trials that can quantify the added value of pharmacogenetic/pharmacogenomic research, the pharmacogenetic complexity of rare variants with unclear functional consequences, the effect of environmental/nutritional factors, and the diversity of the populations worldwide. In this respect, pharmacogenetics and pharmacogenomics (PGx) are emergent fields aimed at tailoring the patient therapy. Both are disciplines with overlapping aims, with the latter being newer and broader than the former. Pharmacogenetics has mainly focused on single genetic variations which can influence responses to drugs (gene-drug pairs), while pharmacogenomics has focused on how all genes, the genome, interact with the action of drugs [1]. Clinical research has demonstrated the cost-effectiveness of pharmacogenetic testing in improving drug compliance in patients, leading to decreased hospital admissions due to adverse reactions to medication [2, 3]. Besides, in the last years, a new promising field has addressed to the study about how environmental factors influence the differential expression of genes related to drug response; this new area is called pharmacoepigenetics [4]. In this chapter, we focus on basic concepts and milestones of these areas.

Human Variability to Drug Response

Human variability to drug response can arise from interindividual differences in ADME processes, rates of drug absorption (A), drug distribution (D), drug biotransformation/metabolism (M),

A. Talevi (ed.), *The ADME Encyclopedia*,
https://doi.org/10.1007/978-3-030-51519-5_124-1



Pharmacogenomics: Basis and Milestones, Fig. 1 The drug phases in the body (from Martínez and Quiñones [5])

and drug elimination/excretion (E), i.e., pharmaceutical, pharmacokinetic, and pharmacodynamic phases [5] (Fig. 1), but also as a consequence of a variety of drug interactions, food-drug interactions, and environmental factors, which may influence safety and efficacy of drugs [6].

Table 1 summarizes the factors that determine the interindividual variation in the response to drugs. In this sense, the proper assessment of drug response requires the analysis of drug properties, patient physiology, and environmentally derived factors.

Pharmacogenetics and Pharmacogenomics

The first historical report of pharmacogenetics dates from 510 B.C., when Pythagoras observed that some people suffered a potentially fatal reaction after ingestion of fava beans [7]. Later, this reaction was related to a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD). Now, this deficiency is related to several adverse effects of some drugs, for example, rasburicase (a drug used for hyperuricemia). Patients with a G6PD deficiency could experience potentially fatal hemolytic anemia [8]. Another example of this adverse reaction is the use of fluoroquinolone antibiotics which is contraindicated in those patients with G6PD deficiency [9]. Another good example of using polymorphism as toxicity marker is the HLA-B*5701 genotype. Patients using abacavir, an HIV reverse transcriptase inhibitor, need to be studied for HLA-B*5701 genotypes, because the patients who carry this variant have a high risk of hypersensitivity reactions, with cutaneous expression and life risk [10].

The discipline that brings together the different studies mentioned above is pharmacogenetics, a term used for the first time in 1959 by Friedrich Vogel [11]. This discipline focuses on studying

Pharmacogenomics: Basis and Milestones, Table 1 Factors conditioning the interindividual variation in the response to drugs. (Adapted from Quiñones et al. [6])

Drug
1. Quality. 2. Physicochemical, pharmacokinetic, and pharmacodynamic characteristics. 3. Type of excipients used. 4. Posology. 5. Route of administration. 6. Interaction with other drugs.
Patient
1. Genetic factors: Transporter efficiency, enzyme metabolic activity, receptor sensitivity. 2. Epigenetic factors: CpG islet methylation, histone acetylation, miRNA expression, and others. 3. Physiological factors: Age, sex, pregnancy-lactation, kidney and liver function. 4. Pathological factors: Kidney, liver, or other diseases. 5. Psychological factors: Placebo effect.
Environment
1. Diet: Consumption of caffeine, meat, vegetables. 2. Alcohol intake. 3. Cigarette smoke. 4. Pollutants.

CpG, GC-rich region; miRNAs, micro-RNAs

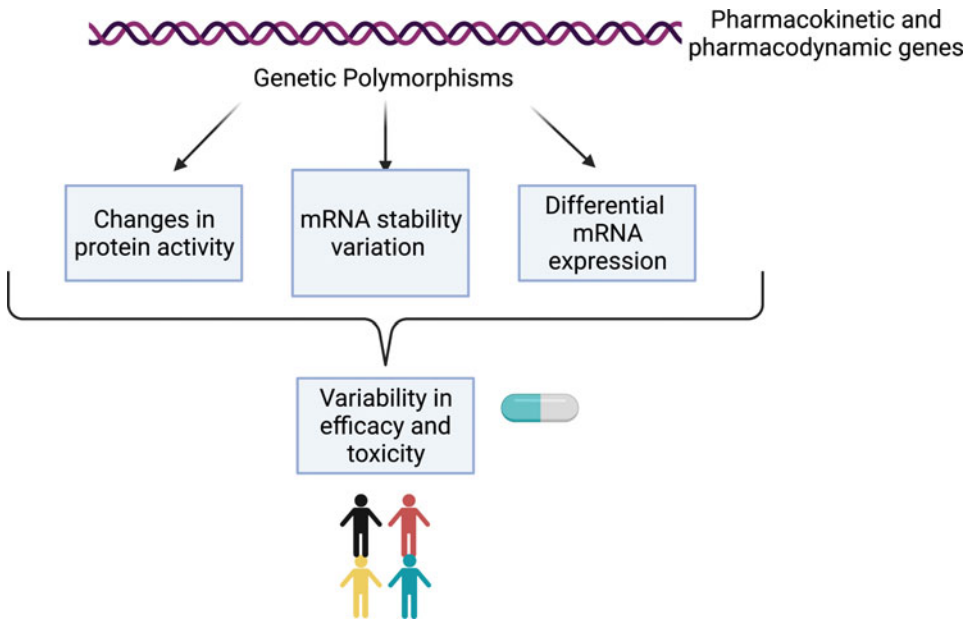
how genetics influences the metabolism and response of drugs [12]; in other words, it refers to the effects of individual genetic variants associated with the pharmacokinetics and pharmacodynamics of drugs [13]. Over time, new technologies appeared that have allowed the description of the human genome variants (next-generation sequencing (NGS), microarrays, qPCR, and digital PCR, among others), favoring the appearance of new disciplines known as "omics," which allow associating more than one factor to an effect. In this sense, the term pharmacogenomics has been coined and refers to the collective influence of variability in the genome that can be associated with an individual profile of response to a drug [12–14]. Pharmacogenomics study the impact of germline but also somatic genetic variations (genotype) on drug response and the incidence of adverse drug reaction (ADR) phenotypes in an individual [2] (Fig. 2).

There is no single approach associated with pharmacogenetics/pharmacogenomics since it depends on both the type of disease and the type of drug treatment. Some of the main lines of studies include the determination of genetic risk factors for the development of diseases [15–18] and the association of genetic variants with response to drugs [19, 20], among others. Additionally, there are studies focused on the association of genetic variants with the exposure of other elements, such as heavy metals, aromatic hydrocarbons, or pesticides [21, 22].

Furthermore, at present, some expert organizations, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) [23] and the Dutch Pharmacogenetics Working Group (DPWG) [24], provide guidelines for PGx clinical implementation of actionable variants (drug-gen pairs) [25]. In addition, other organizations such as the European Pharmacogenetics Implementation Consortium (EU-PIC) [6], Ubiquitous Pharmacogenomics (U-PGx) [26], the Latin American Network for Implementation and Validation of pharmacogenomics guidelines (RELIVAF) [27], and Southeast Asian Pharmacogenomics Research Network (SEAPharm) [28] strive to provide pharmacogenetically guided dosage recommendations.

In this sense, CPIC has generated recommendation guidelines associating genetic variants with drugs, for example, warfarin, in 2011, which incorporates variants for *CYP2C9* and *VKORC1* genes for adjusting the dose according to the genotype obtained. This guideline has been updated according to the new relevant scientific evidence, and to date variants for CYP4F2 have been incorporated. Besides, a differential dose has been established between adult and pediatric patients [29, 30].

Such studies may lead to generation of predictive algorithms of drug response [31–33], which, after validation, may be included in the clinic as a routine prior to drug administration. For example, Martínez et al. (2020) generated a preliminary algorithm for a cohort of patients with hematological cancer that includes genetic variants of the *TLR2*, *IL-6*, *CYP3A4*, and *OAT4* genes, in conjunction with clinical/demographic variables such as type of chemotherapy, diagnosis, days of neutropenia, and age, among others [32]. Although a



Pharmacogenomics: Basis and Milestones, Fig. 2 Pharmacogenetic mechanisms and variability to drug response

validation of this algorithm is needed, this type of study marks a milestone in the application of pharmacogenetics, allowing to improve the quality of life of patients, reducing economic costs and optimizing resources.

One of the databases that compile the studies in this discipline is the Pharmacogenomics Knowledge Base (PharmGKB). With this tool, it is possible to concentrate all the studies associated with the same drug, to identify genetic variants with the highest clinical impact, and to identify if there is any associated clinical guide, among others [25]. On the other hand, the US Food and Drug Administration (FDA) has generated a compilation table of pharmacogenomic biomarkers. This table indicates the drug, its therapeutic area, and the associated biomarkers. For example, CYP2D6 is a FDA-recognized biomarker associated with various drugs, mainly psychiatric ones [34].

All these studies point to the concept of personalized medicine which, although associated to pharmacogenetic or pharmacogenomic factors, also encompasses nongenetic factors. Personalized medicine consists of "focusing the treatment on the patient, not the disease" or, in other words, "two patients with the same disease should not be treated with the same drug or dose." This branch of medicine not only includes genetic factors but also anthropometric (age, weight, and height, among others), clinical (concomitant diseases and pharmacological treatments other than the main disease, among others), and, even, environmental (smoking habit, alcoholic habit, and geographic location, among others) factors [1, 35].

Polymorphism

The common factor of all these studies is the main role given to genetic polymorphisms (Fig. 3). When a genetic variant generates at least two phenotypes having an allele frequency higher than 1% in a population, it is known as a genetic polymorphism [36].

The most common type of polymorphism corresponds to the change of a single nucleotide (SNP, single nucleotide polymorphism), that is, change of one nucleotide for another in the same position. This change, depending on the area in the DNA where it is located, might result in different phenotypes due to amino acid changes, conformational modifications, alterations in gene

expression, or truncated proteins. When a SNP is in a coding region, three changes can occur: (a) a synonymous substitution, when the change generates the same amino acid (usually, when the change occurs in the third nucleotide of a codon); (b) a missense substitution, when the change generates an amino acid change affecting the protein structure; and (c) a nonsense substitution, when the change generates a stop codon, generating a truncated protein [5].

Another type of polymorphism corresponds to insertions and deletions of a few base pairs (InDels). In this case, the variation of the number of bases can trigger changes in terms of structure, function, or expression level of the mRNA [5].

Copy number variation (CNV) is another type of polymorphism that generates a change in the amount of protein. If there is an increase in copies of a gene, the amount of associated protein increases, whereas if there is a decrease in the number of copies, the amount of associated protein decreases. This type of polymorphism, associated with pharmacogenetics, may involve a change in the pharmacokinetics or pharmacodynamics of the drug [5].

Finally, a type of genetic polymorphism known as variable number of tandem repeats (VNTR) corresponds to repeated sequences in the genome that can vary in number between people. Unlike CNVs, these are small sequences that are part of the gene. It has been described that this variant is mainly found in the promoter region of genes, which leads to modifications in the expression of associated proteins [37].

One of the enzyme groups of greatest interest in this area is the cytochrome P450 (CYP) phase I biotransformation system. Many drugs and chemical compounds, including endogenous, environmental pollutants or drugs, are metabolized by these enzymes. These are highly polymorphic isoenzymes, listed and detailed online in PharmVar database (https://www.pharmvar.org) [38], where a compilation was generated that allows searching and identifying the nomenclature of CYPs and their variants. Through studies carried out with the various CYPs, a consensus was reached that there are four phenotypes associated with drug metabolism:

- *Poor metabolizers* (PMs): those subjects that present both defective alleles, and, therefore, there is no enzymatic activity.
- *Intermediate metabolizers* (IMs): those subjects that present a heterozygous genotype or carrying two alleles resulting in an enzyme with decreased activity.
- *Extensive metabolizers* (EMs): those subjects that present both functional alleles, that is, they do not affect the enzymatic activity.
- *Ultrarapid metabolizers* (UMs): those subjects that present more than two copies of the gene. They are generally associated with a CNV.

This characterization has allowed associating an enzymatic phenotype with a clinical picture, that is, with the response observed in patients to drug treatment [5, 38], allowing the clinician to better understand why one patient responds to a treatment and another does not.

Epigenetics

One of the new study approaches of this century is how the environment can modulate the expression of genes, which is known as epigenetics. This research field studies the set of chemical processes that modify the activity of DNA, without altering its sequence [39]. There are three characteristic mechanisms: DNA methylation, histone modification, and noncoding RNA (ncRNA).

Methylations in DNA are incorporated into cytosines (MeC) present mainly in CpG islands and are mediated by methyltransferases. In general, it has been described that the amount of methyl groups in DNA is inversely proportional to genetic expression. As an example, if a gene has hypermethylation in the promoter area, its expression decreases, reaching the point of being completely silenced. Methyl groups are highly stable, but alternative models of demethylation have been included in recent years. One of them indicates that to demethylate a cytosine, it must undergo deamination, generating a thymine; this change is repaired by the base excision repair (BER) system, changing thymine for a

non-methylated cytosine [40]. This mechanism has been described as active DNA demethylation [41].

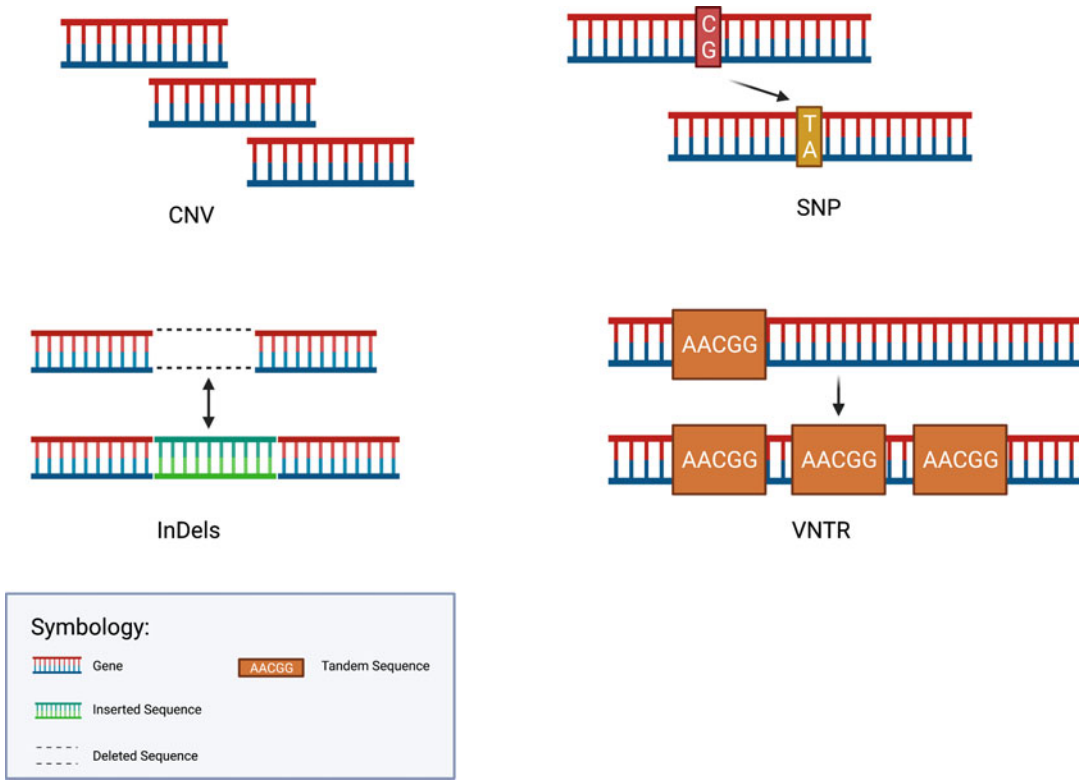
Posttranslational histone modifications correspond to acetylation, deacetylation, methylation, and demethylation reactions. Certain modifications have been associated with an effect, but it is more correct to speak of a modification pattern, since this perspective includes the various histones and the various amino acids with modifications [42, 43].

Finally, the ncRNAs correspond to noncoding RNA sequences of various sizes and origins: microRNAs (18–25 nt), small RNAs (20–300 nt), and lncRNAs (long noncoding RNAs, 300–10,000 nt). They fulfill several functions, among which we can mention inactivation of sex chromosomes, modulation of transcription, and modification of mRNA, among others [39]. MicroRNAs (miRNAs) are of high interest, since they have been associated with multiple mRNA regulations in various diseases and pathways, with cancer being one of the main areas of study [44].

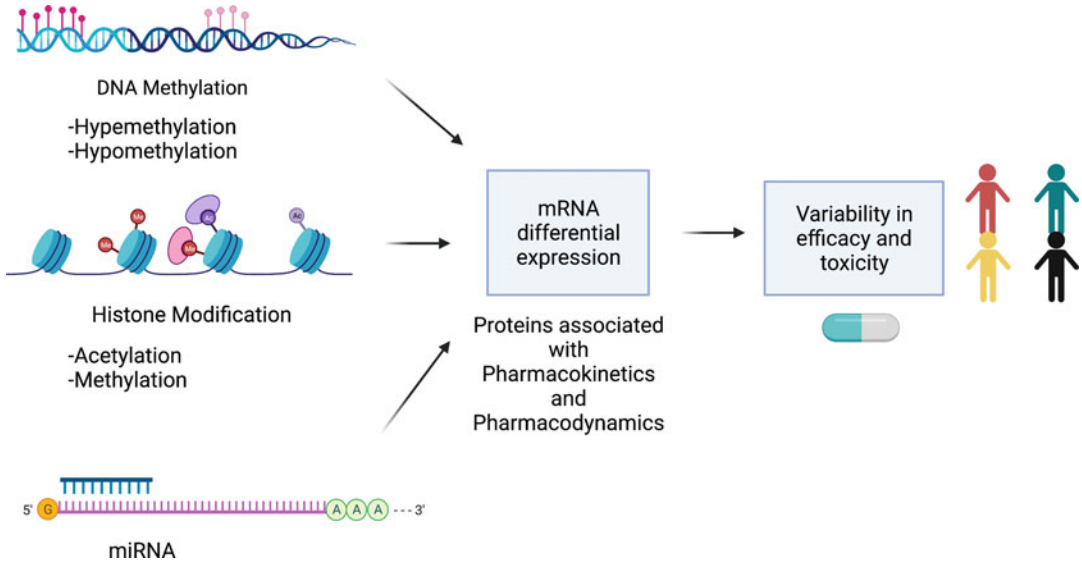
Pharmacoepigenetics

Within the areas of study of epigenetics, pharmacoepigenetics studies nongenetic regulatory mechanisms of enzymes and transporters associated with pharmacokinetics and pharmacodynamics of drugs [45]. These modifications can influence both the efficacy and toxicity of drugs, generating a differential expression dependent on the epigenome present in the study cells (Fig. 3) [4].

In recent times, studies in this area have increased, mainly associated with chemotherapeutic drugs used in breast, ovarian, and gastrointestinal cancer. For example, it has been observed in in vitro breast cancer studies that cells with



Pharmacogenomics: Basis and Milestones, Fig. 3 Types of genetic polymorphisms. CNV, copy number variation; SNP, single nucleotide polymorphism; VNTR, variable number in tandem repeats; InDels, insertion-deletions



Pharmacogenomics: Basis and Milestones, Fig. 4 Pharmacoepigenetic mechanisms and variability to drug response

resistance to doxorubicin overexpress ABGC2, a multidrug-resistant transporter (MDR), and this overexpression is associated with hyperacetylation of histone 3 (H3) near to gene promoter [46]. Another example is that observed with drugs such as 5-fluorouracil and oxaliplatin (FOLFOX scheme), the main therapy in colorectal cancer (CRC). It is known that overexpression of genes encoding dihydropyrimidine dehydrogenase (DPYD); thymidylate synthase (TYMS); methylenetetrahydrofolate reductase (MTHFR); the DNA repair enzymes ERCC1, ERCC2, and XRCC1; and the phase 2 enzyme GSTP1 impairs the response to FOLFOX. Several studies have shown that this regulation may be associated with miRNAs and in turn associated with epithelial mesenchymal transition, which together can lead to chemoresistance (Fig. 4) [47].

As mentioned above, CYPs are isoenzymes that metabolize many drugs, which is why they have been constantly studied. In recent years, they have been associated with epigenetic mechanisms able to modulate their expression. For example, it has been determined that DNA methylation can influence the expression of some CYP associated with the metabolism of endogenous compounds. Similarly, it has been observed that some CYPs, such as CYP1A1, are affected by aberrant methylation of DNA in cancer cells. On the other hand, it was determined that some miRNAs, associated with cellular processes, such as proliferation, morphogenesis, apoptosis, and differentiation, can control the differential expression of CYPs observed between individuals [48]. These studies affirm the idea of incorporating the analysis of epigenetic mechanisms in conjunction with the determination of genetic polymorphisms.

New technologies can be incorporated in the future for the examination of the epigenome, which will support genetic testing. This would allow us to include several relevant factors to determine or predict the behavior of the patient to drug treatment. Identification of new molecules, genetic variants, or epigenetic mechanisms as new biomarkers, could be used to improve the drug response and patients' quality of life and to reduce economic costs [45].

Conclusions

- Since 1959, when Vogel ventured into this area, to date, pharmacogenetic/pharmacogenomic research has become of great impact at the clinical level.

- The main purpose is to determine risk factors, adjust doses, or change medications, according to the patient's genetics, allowing to improve the quality of life of patients. In other words, they are established as the basis of personalized medicine.
- In addition to genetics, clinical/demographic factors have been incorporated to personalize the pharmacological response associated with the drug and the disease, giving rise to polygenic score, pharmacogenomic algorithms, or predictive models for using in precision medicine.
- Today, the study of epigenetic mechanisms associated with enzymes and drug transporters can be incorporated as a new variable capable of determining interindividual pharmacokinetics and pharmacodynamics.

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