Research, Society and Development, v. 11, n. 17, e44111738884, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i17.38884

Pharmacogenomics: an opportunity for safer and efficient pharmacotherapy

Farmacogenômica: uma oportunidade para uma farmacoterapia mais segura e eficiente

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Received: 12/02/2022 | Revised: 12/13/2022 | Accepted: 12/14/2022 | Published: 12/19/2022

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Abstract
Responses to drugs are influenced by multiple factors, including health status, environmental influences, and genetic characteristics. The bioavailability of a drug can vary widely among individuals with a similar weight under the same drug dosage, which might result in toxicity and adverse drug reactions (ADRs). Genetic polymorphisms are known causes of interindividual differences in disease risk and treatment response in humans. In fact, a relevant number of associations between human genetic variants and predisposition to adverse events were described for diverse kinds of drug interactions, involving hundreds of proteins like receptors, transporters, and metabolizing enzymes. In this way, Pharmacogenetics and Pharmacogenomics emerged aiming to determine the genetic component responsible for drug response. A particular attention is showed if a treatment benefits (or harms) a particular subgroup, considering the interaction between treatment and genetic background. In this scenario, researchers have focused on better understanding personalized medicine, which holds the potential to maximize drug efficiency and minimize toxic effects. This review aims to introduce some principles, perspectives, and clinical applications of pharmacogenetics, emphasizing important findings and clinical applications that may contribute to therapeutical improvement.
Keywords: Genetic polymorphisms; Pharmacogenetics; Pharmacogenomics; Adverse drug reactions; Personalized medicine.

Resumo
As respostas aos fármacos são influenciadas por múltiplos fatores, incluindo estado de saúde, influências ambientais e características genéticas. A biodisponibilidade de um fármaco pode variar amplamente entre indivíduos com peso semelhante sob a mesma quantidade de fármaco, o que pode resultar em toxicidade e reações adversas aos fármacos (RAFs). Polimorfismos genéticos são causas conhecidas para as diferenças interindividuais no risco para desenvolvimento de doenças e na resposta ao tratamento farmacológico. Um número relevante de associações entre variantes genéticas humanas e predisposição aos eventos adversos tem sido descrito para diferentes tipos de interações medicamentosas, envolvendo centenas de proteínas tais como receptores, transportadores e enzimas metabolizadoras. Dessa forma, a Farmacogenética e a Farmacogenômica surgiram com o objetivo de determinar o componente genético responsável pela resposta aos fármacos. Uma atenção é dada para se um tratamento beneficia (ou prejudica) um determinado subgrupo de pessoas, considerando uma interação entre o tratamento e o histórico genético da população. Nesse cenário, os pesquisadores têm se concentrado em entender melhor a medicina personalizada que tem o potencial de maximizar uma eficiência dos fármacos e minimizar os efeitos tóxicos. Esta revisão visa apresentar alguns princípios, perspectivas e aplicações clínicas da farmacogenética, enfatizando achados importantes e aplicações clínicas que podem contribuir para o aprimoramento terapêutico.
Palavras-chave: Polimorfismos genéticos; Farmacogenética; Farmacogenômica; Reações adversas a medicamentos; Medicina personalizada.

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Resumen

Las respuestas a las drogas están influenciadas por múltiples factores, incluido el estado de salud, las influencias ambientales y las características genéticas. La biodisponibilidad de un fármaco puede variar ampliamente entre individuos de peso similar bajo la misma cantidad de fármaco, lo que puede provocar toxicidad y reacciones adversas a drogas (RADs). Los polimorfismos genéticos son causas conocidas de las diferencias interindividuales en el riesgo de desarrollar enfermedades y la respuesta al tratamiento farmacológico. Se ha descrito un número relevante de asociaciones entre variantes genéticas humanas y predisposición a los eventos adversos para diferentes tipos de interacciones medicamentosas, involucrando a las proteinas como receptores, transportadores y enzimas metabolizadoras. Así, la Farmacogenética y la Farmacogenómica surgieron con el objetivo de determinar el componente genético responsable de la respuesta a las drogas. Se presta la debida atención a si un tratamiento beneficia (o perjudica) a un subgrupo de personas, considerando una interacción entre el tratamiento y los antecedentes genéticos de la población. En este escenario, los investigadores se han centrado en comprender mejor la medicina personalizada que tiene el potencial de maximizar la eficacia de las drogas y minimizar los efectos tóxicos. Esta revisión tiene como objetivo presentar algunos principios, perspectivas y aplicaciones clínicas de la farmacogenética, enfatizando hallazgos importantes y aplicaciones clínicas que pueden contribuir a la mejora terapéutica.

Palabras clave: Polimorfismos genéticos; Farmacogenética; Farmacogenómica; Las reacciones adversas a medicamentos; Medicina personalizada.

1. Introduction

Inter-individual variation in drug response represents a significant issue in the treatment or prevention of any disease or illness. The bioavailability of a drug can vary widely among individuals with a similar weight under the same drug dosage, which might result in toxicity and adverse drug reactions (ADRs) (Ma & Lu, 2011). Iindividual differences in drug responses are often associated with genetic variations in genes encoding metabolizing enzymes, transporters, and drug receptors. This kind of information can help understand inter-individual and inter-ethnical differences in drug response, which can be useful for pharmacotherapy (Chowbay, Cumaraswamy, Cheung, Zhou, & Lee, 2003; Grasmader et al., 2004). Moreover, genetic variations were also used to predict and explain ADRs that cause about 7% of all hospitalizations and the removal of 4% of the new drugs from the market (Lazarou, Pomeranz, & Corey, 1998).

The human genome sequencing identified variations in DNA sequences that can act on susceptibility and development diseases. Genetic variations are common in the general population, and when a variant frequency is higher than 1%, it is called genetic polymorphism (Karki, Pandya, Elston, & Ferlini, 2015). The common forms of genetic polymorphism are: small insertion and deletions (Indel's), single nucleotide substitutions (SNPs), or variable number tandem repeat (VNTR), which can be further classified in microsatellite (repeating sequences of 2-6 nucleotides) or minisatellite (repeating sequences of 10-60 nucleotides) (Schafer & Hawkins, 1998). SNPs are the most common variation randomly distributed in the human genome and, after the Human Genome Project, several polymorphisms were identified and included in public databases, enabling an increased number of genetic association studies that aim to determine whether a variant is associated with a phenotype or disease (Gjerdevik et al., 2020). An increased number of studies have pointed to specific SNPs in the molecular basis of several illnesses, suggesting that those variations can be used as genetic markers. Besides, there was a significant effort from the scientific community to identify and map genomic variability in different populations, resulting in different genomic projects, such as HapMap and one thousand Genomes. As a result, those projects helped understanding the interaction between genetic variants and drug targets in specific populations, previously unknown and responsible for the ADRs. From this interaction emerged the Pharmacogenomics term, an extension of Pharmacogenetics, which encompasses genomics studies related to drug responses (Genomes Project et al., 2010).

In this way, Pharmacogenetics and Pharmacogenomics appeared aiming to determine the genetic component responsible for the drug response. The idea that some genes are important in drug response was suggested in 1950's, from an association between inheritance and ethnic background to aberrant drug response (Evans & Relling, 1999; Lehmann & Ryan,

1956). Ever since, there is a growing literature on previous commercialized drugs describing its efficiency and/or safety based on some genetic variations, which encourages the use of genomic information to the development of new drugs (Roses, 2004). As consequence of the human genome sequencing, Pharmacogenetics and Pharmacogenomics are becoming the field of choice for the discovery of new drugs, which is affecting the structure and economy of the pharmaceutical industry (Bienfait et al., 2022).

Under the same drug dosage, the main causes of inter-individual variability in drug response are age, genetic and immunological factors, pathological stage and drug interactions (Wilkinson, 2005). The known genetics variants responsible for drug response can be classified in two groups: pharmacokinetics (PK) and pharmacodynamics (PD): PK genes affect the mechanisms of the drug's absorbance, distribution, metabolism and excretion; PD genes affect the concentration and effect of the drug and the interaction of the drug with its target (Ross, Anand, Joseph, & Pare, 2012). Genetic variance may act as contributing factors for the efficiency and safety of a drug. Under this thought, both Pharmacogenetics and Pharmacogenomics study the different genetic variations that exist between individuals and populations in order to adjust appropriate treatments to improve the efficacy of drugs and reduce the side effects Pharmacogenomics concentrates on the influence of the genetic variation in drug response, in order to rationally improve pharmacotherapy, ensuring maximum efficiency and minimizing ADRs (Agundez & Garcia-Martin, 2022). This approach anticipates the "personalized medicine", wherein pharmacotherapy will use individuals' genetic information (Nebert, Zhang, & Vesell, 2008; Roses, 2004).

Nowadays, drugs prescriptions are based on medical diagnosis and comorbidities that may guide the physician to prefer one drug instead of other, taking into consideration ADRs and characteristics of the patient, such as age, liver and renal function, pregnancy, and lactation. Currently, therapy prescription does not consider genetic interindividual differences, which could interfere in both efficiency and toxicity of the drug (Johnson & Evans, 2002). It is estimated that only one third of the patients obtain therapeutic benefits from the prescribed drugs, while in two thirds of them, the drug is not tolerated or does not act as expected (Norton, 2001). The clinical addition of Pharmacogenomics brings the possibility of predicting benefits and ADRs from the patients' genetic information. Main examples of Pharmacogenomics emerged from clinical observation in differences on drug responses to standardized drugs dose and from observation on plasmatic and urinary concentration of the drug or its metabolites (W. Zhao & Meng, 2022). In this context, pharmacogenomics can help selecting the most appropriate pharmacological agent for a given patient and help the development of cost-effective treatments (Ross et al., 2012; van der Wouden, Marck, Guchelaar, Swen, & van den Hout, 2022). In this review we will approach the therapeutic implications of genetic differences and the Pharmacogenomics potential to improve drug treatments and its application in pharmaceutical industry.

2. Methodology

A review of the literature was conducted with a bibliographic survey carried out in the databases: International Literature in Health and Biomedical Sciences (PubMed: https://pubmed.ncbi.nlm.nih.gov/) and Virtual Health Library (http://bvsalud.org/). Free access paper or made available in full by UERJ in the CAFe system -RNP (Federated Academic Community and National Network of Teaching and research). were selected and published until November 2022, using the terms: "Pharmacogenetics" AND "Pharmacogenomics" AND "Genetic polymorphisms" OR "Adverse drug reactions" OR "Cancer treatment" OR "Inflammatory diseases" OR "Infectious diseases" OR "Pain management" OR "Cost-effective treatments" OR "Pharmaceutical industry". The literature search yielded 4,360,316 studies. Then, letters to the editor, abstracts published in conferences, articles with retractions and articles not written in English were excluded. The papers considered most interesting were used to elaborate this narrative review of the literature in accordance with Cronin et al., 2008 (Cronin,

Ryan, & Coughlan, 2008).

3. Results and Discussion

3.1 Differences in responses and adverse drug reactions (ADRs)

Drug adverse reactions (DARs) are a health discomfort worldwide and exist a thousand related cases which could be avoided (Cacabelos, Cacabelos, & Carril, 2019). Pharmacogenomic analysis is used to distinguish the phenotypic heterogeneity between population by means of drug sensibility or ADR risk. The pharmacogenomic function is to reduce drug adverse effects (Thong, Vultaggio, Rerkpattanapipat, & Schrijvers, 2021; Yang et al., 2021). In the last decade, there was an earnest effort focused on characterize drug-metabolizing enzymes variations considering ADRs. Over four hundred genes are clinically relevant in drug metabolism (Cacabelos et al., 2019). There are two kinds of ADRs: type A, dose-dependent reactions that can be predicted by excessive dosing; type B, unlike the type A, are idiosyncratic and, usually, do not show any relation to the drug dosage (Edwards & Aronson, 2000). ADRs are also a great issue on the development of a new drug (Gupta et al., 2021).

The search for Pharmacogenomics biomarkers that might be used to identify increased toxic effect risk has been focused on the variation in key pharmacokinetics and pharmacodynamics coding genes (Becker & Leeder, 2010). Polymorphisms on drug-metabolizing enzymes genes can affect phase I (oxidation, reduction and hydrolysis) and phase II reactions (conjugation reactions, acetylation, glucuronidation, sulfation and methylation) (Jaja, Burke, Thummel, Edwards, & Veenstra, 2008). Furthermore, many studies have associated N-acetyltransferase 2 (NAT2) polymorphisms with ADRs after treatment with Caffeine, Dapsone, Isoniazid and Sulfonamide, as well as toxicity effect to Hydralazine treatments (Becker & Leeder, 2010; Collins et al., 2020; Thomas et al., 2022).

3.2 Cytochrome P450 enzymes (CYP) and genetic polymorphisms

CYP enzyme family are responsible for around three-quarters of all drug metabolism reactions that occur in human populations, and it is a multi-gene superfamily of heme-thiolate enzymes encoded by more than 2700 genes. They have important roles in homeostasis, cellular metabolism The enzymes can act on many aspects , for example: in the oxidation of endogenous molecules into hydrophilic compounds, such as eicosanoids, steroids and a high number of drugs, chemical products and environmental pollutants (Krau, 2013). The CYP enzyme family can be responsible for more than 90% of all drug detoxification in humans(Waring, 2020; M. Zhao et al., 2021).

In humans, CYP genes are highly polymorphic, which can have consequence in the enzyme activity or expression, leading to unexpected drug levels that can result in ADRs or low drug efficiency. Drug metabolizer phenotype classifications are based on CYP enzymatic activity, wherein Individuals can be classified in poor metabolizer (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs) and ultrarapid metabolizers (UMs) (Ingelman-Sundberg, 2004).

Even though a great part of this discussion is related to drug metabolism, advances in molecular biology and genomics revealed many processes associated to CYPs. Chemical compound’s metabolism often results in compounds detoxification, however intermediate metabolites generated from this process can be toxic for the organism. Furthermore, identifying metabolites have a crucial role in the drug development (Nebert & Russell, 2002; Wu et al., 2021). There are 57 genes in the human CYP family, whereas CYP1, CYP2 and CYP3 play a crucial role on exogenous compounds metabolism and CYP4 processes endogenous compounds (Nebert & Russell, 2002; Qi et al., 2021; Wu et al., 2021). Almost 50% of all currently available drugs undergo enzymatic biotransformation in the liver by the CYP3A4 system (Mulder et al., 2021; Thummel & Wilkinson, 1998). CYP genes are highly affected by genetic polymorphisms and the polymorphic forms of these enzymes are

very frequent in the population (Chen et al., 2018). Within the CYP superfamily, only CYP1A1 and CYP2E1 are conserved and do not have any functional mutation, in addition to being modulates by hormones (Ingelman-Sundberg, 2001; Kuzgun, Basaran, Arioglu Inan, & Can Eke, 2020).

Regarding Phase I metabolism reactions, genotyping offers a crucial tool for pharmacotherapy improvement, using a few specific drugs. Among those drugs are included: Warfarin (CYP2C9), tricyclic antidepressants (CYP2D6), Codeine (CYP2D6), Pherfenazine (CYP2D6), and Omeprazole treatment (CYP2C19) (Aithal, Day, Kesteven, & Daly, 1999; Fukuda et al., 2000; Gardiner & Begg, 2006; Sagar et al., 2000). Furthermore, CYP2D6 is one of the most important Isoenzyme, once it metabolizers about 24-30% of all prescribed drugs (B. Wang et al., 2009). CYP2D6 has also been related to statin metabolism and the *CYP2D6 * 4* allele was associated to muscular pain linked to Atorvastatin therapy (Frudakis et al., 2007).

Furthermore, it was previously described an association between the *CYP3A4 * 22* SNP with statins metabolism, whereas the SNP carriers require only about 20-60% of the standard dosage of Atorvastatin, Simvastatin and Lovastatin to achieve the ideal lipid profile (Patel, Abd, Blumenthal, Nasir, & Superko, 2014; D. Wang, Guo, Wrighton, Cooke, & Sadee, 2011).

3.3 Cancer treatment and genetics variations

Oncology is one of the medical specialties that work great pharmacological therapy issues. With advances in DNA sequencing, high heterogeneity in cancer genetics was revealed, answering many questions about patients' different responses and predictive biomarkers for sub-groups of cancer patients. Individuals sharing the same kind of tumor might carry different genetics variations, which explain the high range of disparity in response for the same anti-cancer drug therapy, which has a large variability in pharmacokinetic (PK) and narrow therapeutic index (Kristyanto & Utomo, 2010).

Even though Pharmacogenomics and Pharmacogenetics refers commonly to genetic polymorphism that confers interindividual variability in a drug response, there are cases where tumor somatic mutations (i.e. genetic variation found exclusively in the tumor genome) can create specific targets or alter drug response (Kamatani & Nakamura, 2021; Talseth-Palmer & Scott, 2011). For example, for years it has been indicated a specific treatment with Trastuzumab (Herceptin®) and Imatinib Mesylate (Glivec®) for a sub-group of patients with the amplification of the Breast Cancer gene HER2, and the genic translocation BCR-ABL in Chronic Myeloid Leukemia, respectively (Shojaei, Gardaneh, & Rahimi Shamabadi, 2012). These therapies are targeted therapy, which act directly against cancer-specific molecules. Target therapy efficiency depends on accurate detection of the initial target, as well as on the evolution of cancer cells. However, as cancer cells continue to proliferate and accumulate mutations, drug-resistant subclones can appear during the therapy, compromising the efficacy of the treatment (Sabaawy, 2013).

Other targeted therapies such as Tyrosine-kinase inhibitor, Imatinib Mesylate, Gefitinib and others, can also interact with ABCG2/BCRP, an Adenine triphosphate (ATP)-binding cassette (ABC) transporter, member of the ABCG family that is associated with treatment resistance in tumor cell lines. Both functional SNPs and ABCG2/BCRP inhibitory agents can modulate the PD and PK of the targeted therapy. In this way, interactional analysis of the molecular target can indicate the efficiency of combined therapy (Noguchi, Katayama, & Sugimoto, 2014).

3.4 Inflammatory and infectious diseases therapy and genetic polymorphism

As physiopathology of infectious and inflammatory diseases have been elucidating, there is growing evidence that a complex and integrated series of events involving inflammatory mediators can be responsible for the consequences of the diseases (Fontes, de Araujo, Coutinho, Leib, & Agnez-Lima, 2015). Ever since, there is an extensive search for genetic

markers that could help on the diagnosis and understanding of the clinical development of these diseases, as well as on therapy directed to each individual inflammatory response (Schnappauf, 2020). This phenomenon is evident in chronic infections, whereas microorganisms can become resistant to the host immune response. Many genes associated to immune response were analyzed in different populations and immunological control models were proposed to several diseases, such as Bacterial Meningitis and more recently Covid-19 (Anastassopoulou, Gkizarioti, Patrinos, & Tsakris, 2020; Fontes et al., 2015).

There are studies associating inflammatory and infectious disease with efficient drug treatment, ADRs and genetic-related toxic effects. For example, chronic infection with Hepatitis C virus (HCV) is treated with a combined therapy of Pegylated Interferon alfa-2a (PegIFN-α-2a) and Ribavirin. However, less than 50% of treated patients obtain a sustained virological response (SVR) (Feld & Hoofnagle, 2005). Later, a genetic study with 1671 patients diagnosed with chronic HCV reported a SNP in the *IL28B* gene (rs12979860) strongly associated with SVR, which could explain the heterogeneous response of the combined therapy (Ge et al., 2009).

Moreover, Methotrexate (MTX) remains the standard gold drug of choice for the treatment of Rheumatoid arthritis (RA), polyglutamates from the MTX inhibit dihydrofolate reductase and thymidylate synthase, important intracellular enzymes in folic acid pathway. Nowadays, different studies have been focused on SNPs in the folate pathway genes to predict efficiency and toxicity of MTX (Stamp et al., 2010). In this concern, SNPs in adenosine monophosphate deaminase 1 *(AMPD1* 34CT-*rs17602729* aminoimidazole carboxamide ribonucleotide transformylase/inosine monophosphate cyclohydrolase (*ATIC* 347CG-*rs2372536)*), and inosine triphosphate pyrophosphatase (*ITPA* 94CA-*rs1127354*) enzymes (all involved in the cAMP pathway) have been associated with a clinical effective response to MTX during RA treatment (Maksimovic et al., 2020; Wessels et al., 2006).

Inflammatory bowel diseases (IBD) comprehend two main clinical subtypes, Crohn's disease, and ulcerative colitis, both display high morbidity and mortality rates. In addition to diet that might modify environmental risk factor for IBD onset and severity., drugs are used in the IBD treatment include anti-inflammatory agents (5-Aminosalicylic acid, Sulfasalazine, Corticosteroids), immune modifiers (Azathioprine (AZA) and Mercaptopurine-6-mp (6-MP), Methotrexate), anti-TNF agents (Infliximab, Adalimumab, Certolizumab), antibiotics (most commonly, Metronidazole and Ciprofloxacin) and probiotics. Before treatment initiation with AZA or 6-MP thiopurines, phenotyping or genotyping of thiopurine methyltransferase enzyme (TPMT) are recommended to guide drug dosage, maximizing the safety of the patient. TPMT enzyme acts on AZA and 6-MP metabolisms, converting them into inactive metabolites, and genetics variances in this gene can induce myelotoxicity (Sasson, Ananthakrishnan, & Raman, 2021). More than 20 SNPs can reduce TPMT production, hereafter there are the most common alleles among Caucasians: *TPMT*3A* (4.4%), followed by *TPMT*3C* (0.4%) and *TPMT*2* (0.2%).

3.5 Pharmacogenomics of pain management

Genetic association studies of pain variability and analgesic effects modifiers have shown that pain management is also subjected to pharmacogenomics analysis (Veluchamy et al., 2021). Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, as a consequence of a complex heritage, is a polygenic trait influenced by environmental factors (M. Cohen, Quintner, & van Rysewyk, 2018). It has been demonstrated that both, rare variants and common SNPs, are mediators of the human perception of pain and can influence different pain phenotypes (Fillingim, Wallace, Herbstman, Ribeiro-Dasilva, & Staud, 2008).

Genetic information on human perception of pain and its mechanisms can help modulating analgesic therapy. Different analgesic responses can also result from PD interference, including ligand receptor modifications, alterations in receptor binding, or in drug signaling mechanism. So far, only a few variants were identified and most of them produce

secondary effects that can be partially annulled, therefore, genetic variants can still not be used to provide a relevant prediction of individual pain or analgesic response (S. P. Cohen, Vase, & Hooten, 2021; Yamamoto, Conchon Costa, Lauretti, & de Moraes, 2019).

Most of the opioids contain a hydroxyl group at the 6-position, differently than powerful opioids that contain a hydroxyl group at 3-position of the 4,5-methoxymorphine. Glucuronidation of Morphine, Codeine, Buprenorphine, Dihydrocodeine, Dihydromorphine, Hydromorphone, Oxymorphone, as well as opioids receptors antagonists (Naloxone, Naltrexone), are mainly mediated by uridine diphosphate (UDP) and glucuronyltransferase (UGT) 2B7. Similarly, to the CYP genes, the *UGT2B7* is also very polymorphic, although less than 20 allelic variants were identified. The *UGT2B7*2* (268Y) variant was associated with active metabolite production, where about 70% of Morphine is metabolized in morphine-6-glucuronide (M6G), and the remaining 30% is metabolized in morphine-3-glucuronide (M3G). These active metabolites exhibit opposite effects, whereas M6G displays typical opioids agonistics effects and the M3G acts on excitement and anti-analgesia (Somogyi, Barratt, & Coller, 2007).

Currently, as consequence of many inter-individual variations and opioids super dosages, there is a great demand on genetic association studies concerning post-operatory analgesia in children. Recently, it was reported an association of four Catechol-O-methyltransferase (COMT) SNPs (rs6269, rs4633, rs4818 and rs4680) with pain in 149 children, after adenoamigdalectomia surgery. They also demonstrated that variants carriers displayed a higher perception of post-operatory pain, requiring Morphine (Sadhasivam et al., 2014). In addition, the implementation of pharmacogenomics in pain area is extremely important due to development guidelines for several drug-gene pairs, giving evidence in the clinic (Yamamoto et al., 2019).

3.6 Genetic human evaluation might improve studies in pharmacoeconomic

Pharmacogenomics can potentially reduce the costs associated with inappropriate drug treatment or ADR-related hospitalizations. Pharmacoeconomic, a branch of health economics, have been used by Health systems to evaluate the introduction of modern technologies, such as new diagnosis methods, demographic information, and advances in genetic engineering. Financially, pharmacogenomics requires a careful cost-benefit analysis, for example, if a specific SNP only confers a slightly benefit to a drug, the costs associated to an alternative treatment should be carefully evaluated(Ross et al., 2012; Verbelen, Weale, & Lewis, 2017).

An example of genetic test that reduced the cost and improved the efficiency of the therapy is the treatment of HIV-infected patients with Abacavir, a reverse-transcriptase inhibitor. Abacavir hypersensitivity syndrome (AHS) is a potentially fatal side effect that affects 5-8% of the HIV patients, during the first six weeks of treatment (Hetherington et al., 2001). Patients suffering from AHS were strongly associated with the presence of the *HLA-B*5701* variation within the histocompatibility complex class I, which is present in 2-6% of Caucasians (Mallal et al., 2008). Kauf et al. 2010 analyzed the cost-effectiveness of the *HLA-B * 5701* screening by evaluating genetic test costs before the drug treatment, and the usage of alternative treatment with Tenofovir. Their results showed a significant cost decreased when applying *HLA-B * 5701* screening prior treatment recommendation, suggesting that this procedure should become a routine in HIV health care (Kauf et al., 2010).

As a result of excessive costs associated with opioids adverse effects, the usage of pharmacogenomics, as a tool to improve efficiency and reduce adverse results, is currently under evaluation. Candidate *loci* genotyping for opioids adverse effects prevention, or therapeutic failure, follows the Clinical Pharmacogenetics Implementation Consortium, which describes guidelines for dosages based on genotypes to some drugs, like Tramadol, Oxycodone and Codeine (Johnson et al., 2012; Racoosin, Roberson, Pacanowski, & Nielsen, 2013).

Since 2011, more than 400 drugs received FDA approval for including Pharmacogenomics information in their fact sheet (FDA). However, the impact of Pharmacogenomic information relies on the genetic background of the patient and rare mutations still need careful evaluation to fully understand their consequences concerning drug response. That information could optimize the treatment and reduce unnecessary costs in drug treatment. Although, for each specific case, the costs regarding the application of pharmacogenetic tests should be evaluated, advances in genotyping tools and translational sciences will soon facilitate the application of these tests. In this context, the further integration of genomic information and sociocultural dynamics could trigger advances in precision medicine, which will be able to link large genomic research projects with health care programs (Peters, Cooper, & Buchanan, 2015; Tekola-Ayele & Rotimi, 2015).

In terms of the evaluation of cost-effectiveness, it was constructed a decision-analytic model support the clinical impact of medical prescription guided by pharmacogenomics. Their model evaluated Netherlands patients in use of seven drugs (clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine, and irinotecan) for 1-year and was able to reduce gene-drug related mortality by 10.6% and found a cost savings €51,000 per prevented death. In addition, an interesting study reviewed 44 economic evaluations that investigated the cost-effectiveness of pharmacogenetic strategy. The study concluded that pharmacogenetic strategy produced both improved health outcomes and cost savings (van der Wouden et al., 2022).

3.7 Pharmaceutical industry vision on human genetic profile

Besides the identification and validation of new therapeutic targets, one of the many applications of genomics to the pharmaceutical industry is the selection of better drugs to a specific target. The use of genomic information in the development of new drugs and therapies and revolutions in pharmaceutical engineering technology are transforming the healthcare system. Advances in drug discovery involve several areas of healthcare system. The scientific domain includes progress in medical sciences through systems biology, using genomic information in clinical practice by means of individual drug therapy. The society domain is determined by the availability, access and use of information in personal drug therapy (Stegemann, 2016).

Development of new drugs brings several challenges to the pharmaceutical industry, concerning to identify which group of patients will have similar adverse reactions based on their genetic profile. Moreover, biotechnological progresses provide a new perspective into the discovery and development of biological compounds like proteins, monoclonal antibodies (Mabs) and siRNAs, creating a novel targeted and personalized medicine (Annett, 2021; Hecht et al., 2015; Weng et al., 2020). Additionally, epigenetic regulation that influences the expression of various drug-metabolizing enzymes also provides an important mechanism that can contribute to inter-individual variability in drug metabolism and efficacy (O'Rielly & Rahman, 2015).

Pharmaceutical industry has shown a great interest in establishing a partnership with the public sector, aiming to develop a human genome SNP map (International Warfarin Pharmacogenetics et al., 2009). From that partnership it was created the *SNP Consortium,* a nonprofit association formed by the Wellcome Trust and ten pharmaceutic companies, including *AstraZeneca, Bayer, Pfizer, SmithKline Beecham, Roche* e *Novartis,* that aimed to map 300 common SNPs in the human genome in the next years (Destenaves & Thomas, 2000). Using information on drug responses and pharmacogenomics, the pharmaceutics industry could encourage evaluation tests on the therapeutic efficiency of a drug at the initial phase of the treatment. As a consequence, this could efficiently select new compounds that can treat a group of patients with the same disease and characteristics, and further develop three or four molecules that could specifically cover most of the patients, instead of prescribing a periodic treatment with several drugs (Ross et al., 2012).

4. Conclusion

The practical Pharmacogenetics and Pharmacogenomics application in the investigation and development of drugs is not simple. These novel approaches will affect both patients interested in their genomic information and physicians that do not comprehend the genetic basis of some disease, and therefore will find difficulties in prescribing drugs based on the patients' genotypes. Besides, these approaches will also influence the industry, which may not have the required technology for the development of drugs based genetic information. As consequence of the difficulties, the industry might launch highly cost drug in the market.

Moreover, technologies advances will reduce genotyping costs earlier than the establishment of polygenic models. In long term, decreased frequency of ADRs and increased therapeutic success will reduce the costs with health care. Pharmacogenomics can potentially facilitate the translational process of identifying human genome variants and use this information to improve drug therapy, launching a new era of pharmacotherapy with more efficient and safer drugs (Ross et al., 2012). Personalized medicine may help guiding individual treatment, once is expected that the risk-benefit of a drug vary according to genotypes. As a result, such variations may compromise safety and treatment efficiency. Adverse responses can differ accordingly to genotypes groups; for example, slow metabolizers can accumulate toxic metabolites. In this way, patients' genotype information can be used to guide clinical decisions, since the patient might benefit from an alternative pharmacotherapy (Johnson et al., 2012).

Pharmacogenomics and Pharmacogenetics integration with clinical care has been a challenge for many reasons, including inability in defining phenotypes for drug/response/toxicity distribution, lack of profitable tests and lack of a software that integrates in an Electronic Health Record (EHR) (Destenaves & Thomas, 2000).

The Clinical Pharmacogenomics service of the National Institutes of Health Clinical Center (NIH-CC), gathered by a Multiprofessional Implementation Committee, was created to develop an algorithm that could assist the clinical decision of the treatment with Abacavir, Carbamazepine and Allopurinol. The Pharmacogenetic test implementation was a NIH-CC initiative that holds the responsibility of assuring appropriate tests and training professionals' team. After the patient's genotyping, the results would be available for future Pharmacotherapeutic decisions (Goldspiel et al., 2014; Tippenhauer, Philips, Largiader, Sariyar, & Burkle, 2020). In Brazil there is the Rede Nacional de Farmacogenética (REFARGEN) established in 2003, a consortium of research groups from different Brazilian institutions, which is an initiative aiming to promote and coordinate integrated projects of pharmacogenetics/pharmacogenomics research in the Brazilian population, impacting on the health system (www.refargen.org.br).

Pharmacogenetics and Pharmacogenomics provide a promising future once personalized medicine can maximize drug efficiency and minimize toxic effects. Nevertheless, gathered effort with biostatistician, epidemiologist, pharmacists and physicians is required to answer many questions that support individualized treatment to a safer and efficient drug development (Ross et al., 2012). Even though, the final goal of Pharmacogenomics is to develop personalized therapy for a group of patients based on their genetic profiles, identifying genetic polymorphism can also be useful to improve healthcare of a specific population.

Acknowledgments

We thank FAPERJ, CAPES, and CNPq for their financial support.

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