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Pharmacogenomics: History, Development and Challenges

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ABSTRACT

Pharmacogenomics is seen as the combination of pharmacology and genomics. It studies the effect of genetic variations and genetic polymorphisms on the drug response. Individuals respond differently to drugs and sometimes the effects are unpredictable. Differences in DNA that alter the function or expression of proteins that are targeted by drugs can contribute notably to variation in the responses of individuals. This intersection of genomics and medicine has the capacity to yield a new set of molecular diagnostic tools which can be used to optimize drug therapy. By optimizing drug therapy, reducing adverse drug reaction events, and developing patient-centric approaches, pharmacogenomics can achieve the goal of personalized medicine wherein the right drug or right amount of drug is given to the right patient. The present article sheds light upon the historical perspective of pharmacogenomics and the seminal studies examining the fact that patients do not uniformly respond to medications. It also emphasizes the current status of pharmacogenomics and drug development. Some of the barriers in implementing pharmacogenomics have also been presented.

Key Words: *Pharmacogenomics, Adverse drug reactions, Drug Development, Personalized Medicine, Pharmacogenomic Testing*

1. INTRODUCTION

Pharmacogenomics essentially refers to the altered drug response due to genetic variations in an individual. The term "Pharmacogenetics" was first coined by Friedrich Vogel in 1959.1 In the late 1990s, with advancements in DNA technology and genomic sciences, "pharmacogenomics" a newer term was introduced [1]. Both terms are used interchangeably, with pharmacogenetics alluding to the study of individual gene-drug interactions whereas Pharmacogenomics is a comprehensive term for investigating genomic influence on drug response, using high-throughput techniques such as expression profiling, sequencing, single nucleotide polymorphism chip, and proteomics [20]. It identifies genetic factors and their contribution to the interindividual variability in drug efficacy and toxicity. Genetic variations in drug metabolism were first discerned by noticing the very high or very low concentrations of the drug found in some patients despite administrating the same amount of the drug [3]. Variability in drug response arises due to several reasons; the inability of selected drug therapy to target the underlying mechanism which might or might not be known, diseased conditions, drug interactions, lack of compliance, improper drug delivery, changes in the dose are often quoted [4, 5]. However, the genetic architecture of an individual plays a chief role in determining the drug response. Genetic variations influence drug response and can elicit differences in drug response that varies from potentially life-threatening adverse drug reactions at one end of the spectrum, to a lack of desired therapeutic effect at the other end [6,7]. The essence and effectiveness of personalized medicine could possibly circumvent these differences and facilitate the development of personalized therapy to maximize drug efficacy and minimize drug toxicity. From discovering adverse drug reactions due to inherited genetic deficiencies to the present genome-wide approaches assessing genetic variation in multiple genes, the convergence of rapid developments in pharmacogenomics has furnished a pioneering opportunity to move towards the goal of developing truly individualized drug therapy [8]. The concomitant study of the human genome project and the HapMap project has allowed pharmacogenomics to ascertain the altered drug metabolism seen in individuals and specific types of populations [9,10].

Why Pharmacogenomics?

The potential therapeutic effects of pharmacogenomics are immense, and they will minimize the likelihood of adverse pharmacological effects in a patient [11]. The one-size-fits-all model will not provide effective treatment to patients is perspicuous. Doctors will be able to provide optimal and safe therapies to the patients if they have accurate and reliable

pharmacogenomic data. The critical considerations in the field of pharmacogenomics include pharmacokinetics and pharmacodynamics [12]. Polymorphisms in drug metabolizing enzymes ultimately reflect the pharmacokinetics and pharmacodynamics aspects of an individual [13]. Predicting the adverse drug reactions contingent on the above aspects is the priority of pharmacogenomics. The ultimate promise of pharmacogenomics is to improve patient outcomes and reduce overall health costs.[14,15] For instance, Clopidogrel [antiplatelet agent] is bioactivated by CYP2C19 [16]. It has been manifested those individuals having CYP2C19 loss-of-function allele show a decreased response to the drug consequently increasing the incidence of adverse cardiac events compared with non-carriers [17]. Therefore the appropriate dosing recommendations derived from the elucidation of CyP2C19 genotype for clopidogrel are distinctly demarcated in the CPIC instruction [18].

The escalating need for pharmacogenetics has been perceived by FDA and FDA has started implementing the pharmacogenomic information into drug labels and provides a list of drugs for which biomarkers are encompassed in the labeling [19]. Also, the labels provide certain actions which can be carried based on the biomarkers. Moreover, a growing number of institutions have started to develop clinical services and infrastructures to facilitate pharmacogenomic research, analysis, and testing [20] [21]. Although there are numerous challenges to bringing pharmacogenomics into routine clinical practice, the coming years will witness this new paradigm of "Personalized Medicine".

2. HISTORY OF PHARMACOGENOMICS

In early 510 BC, the Greek Philosopher and mathematician Pythagoras first noted the adverse response when he observed that certain Mediterranean populations developed favism, a form of hemolytic anemia and jaundice ensuring the intake of fava beans and other legumes [22]. It was later discovered that favism was a result of a hereditary abnormality leading to deficiency of the red cell enzyme Glucose-6- phosphate dehydrogenase [G6PD] [23]. The prior probing and pioneer studies include the establishment of rules of heredity by Mendel in 1866, Characterization of the 'phenylthiourea nontaster' as an autosomal recessive trait in 1932 [24], and ascertainment of sensitivity to the hemolytic effect upon the administration of primaquine, an antimalarial drug was due to intrinsic defect in erythrocyte leading to deficiency of G6PD enzyme during World War 2 [25–27]. All these studies were summarized and revised by Dr. Arno Motulsky and he published a paper titled 'Drug reactions, enzymes, and biochemical genetics' in 1957 [28]. The 20th century profusely witnessed numerous research being conducted on various drug-metabolizing enzymes and assessing the contribution of the various genetic components to the overall response to a drug [29,30]. In the 1960s Karlow demonstrated the prolonged response to the muscle relaxant succinylcholine causing apnea and long muscle paralysis due to a genetically determined defect in Butyrylcholinesterase [pseudocholinesterase] which inactivates succinylcholine in a few minutes [31]. His other influential studies lead to the publication of the book "Pharmacogenetics: Heredity and the Response to Drugs" in 1962 underlying the significance of interindividual variations in drug response [32]. In 1962, Vogel coined the term 'Pharmacogenomics'. Another seminal study includes the illustration in the polymorphism in human NAT [N-acetyl transferase] enzyme relevant in the pharmacokinetics of drugs like hydralazine [hypertensive] and isoniazid [antitubercular] by Price Evans [33]. This is majorly found in Caucasian populations [34]. He found out that there are two variants of the human NAT isoenzymes now known as NAT1 and NAT2 which catalyzes N acetylation and O-acetylation of heterocyclic amines and arylamines [35]. 'Slow acetylations and 'fast acetylations aroused from the polymorphism in NAT affected the Pharmacokinetics of certain drugs [36]. Slow acetylators lead to high plasma levels of drugs such as hydralazine and isoniazid which enhanced their toxicity whereas the fast acetylators showed an altered response to the treatment than anticipated. In 1988, The polymorphism in debrisoquine hydroxylase now known as CYP2D6 was another pertinent observation in the metabolism of debrisoquine and sparteine [37,38]. Gonzalez and Meyer cloned the enzyme and characterized the defect in it [39–41]. Subsequently, it was found out that certain individuals were referred to as poor metabolizers and rapid metabolizers [42,43]. The toxicity of the drug was increased in PMs whereas the efficacy of the drug was decreased in RMs [40,42,43].

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3. CURRENT STATUS OF PHARMACOGENOMICS

Pharmacogenomic knowledge is being used extensively to develop tailored drugs to treat a wide range of health problems. An instance of its application involves patients affected with Human Immunodeficiency Virus [HIV]. Patients who carry the HLA-B*5701 variant are susceptible to developing an adverse hypersensitivity reaction to the drug abacavir [52,53]. Hence, before prescribing abacavir, doctors routinely test for the variant and the drug is contraindicated if the test is positive [54]. It has been recommended by FDA that doctors should test colon cancer patients for certain genetic variants before administering irinotecan [Camptosar], which is part of a combination chemotherapy regimen [55,56]. Another instance is the drug trastuzumab used to treat breast cancer. This therapy is effective in women whose tumors possess a specific genetic profile which leads to overproduction of HER2 protein [57,58]. Genetic testing of the patients before administrating mercaptopurine, a chemotherapy drug to be used to treat acute lymphoblastic leukemia is recommended by FDA [50,59,60]. The aim of pharmacogenomics is to elucidate the gene-drug interaction, to find out the genetic variants responsible for the lack of desired response, and to deliver efficacious therapies [61,62].

Table1. Pharmacogenomics: Seminal Studies

Drug	Altered Clinical Effect	Gene Responsible	Mechanism	Reference
Primaquine	Haemolytic Anaemia	G6PD	G6PD deficiency	[27]
Phenylthiourea	Impotence to taste PTU	TAS2R1	PTU non-taste trait, SNPs in taste receptor	[44,45]
Isoniazid	Peripheral neuropathy in slow acetylators	NAT2	Altered function, variations in NAT2	[46,47]
Debrisoquine	Poor metabolizers showed ADR	CYP2D6	CYP2D6 variants	[40,48,49]
Thiopurines	Myelosuppression in poor metabolizers	TPMT	TPMT variants result in reduced function	[50]
Succinylcholine	Prolonged muscle paralysis	Butyrylcholin esterase	Reduced BChE activity	[31,51]

4. PHARMACOGENOMICS IN DRUG DISCOVERY

Remarkable advancements in genome sequencing technology have enabled pharmaceutical companies to formulate futuristic models and suitable computational and informatics studies supporting them [63,64]. Researchers are twice as likely to find a drug target utilizing genomic knowledge and computational support than utilizing old methods [65,66]. The elucidation of drug targets could be improved by genetics by ameliorating the design of clinical trials and as a consequence drugs could possibly get to the market quickly [67,68]. In addition, during clinical trials, it could assist in predicting the drug response based on the personalized testing of variants [67,69,70]. Moreover, researchers are engrossed in contriving and validating tests for subsequent clinical applications. Connecting the gene with the disease and obtaining a molecule that can be amended to treat the disease is the preliminary step. [71] The pharmacokinetics and pharmacodynamics of new drugs are well articulated by scrutinizing

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pharmacogenomic studies, and these advancements impact the development of new drugs [30,67]. Targets that succeed during the target validation process are probably genetically validated. Although we have only 10 to 15 percent of targets that possess genetic data on them, and they ultimately result in the reduction of cost [70,72]. This can be achieved by interpreting human genetics and by outlining less expensive clinical trials [33,73]. The therapeutic risk and benefit ratio is improved by decreasing side effects in patients during clinical trials [1,73,74]. Clinical shreds of evidence for research and drug development and all the needful information are offered by pharmacogenomic studies to proceed into the next steps of the process [64,73,74]. Scientists will thus be able to determine the most responsive patients and will make the drug development process more reliable. Hence, scientists are adapting to this new paradigm which works towards the development of precision medicine [75,76].

5. PHARMACOGENOMICS, DRUG DEVELOPMENT, AND FDA

As a part of the drug development process, the pharmacogenetic data submitted by the pharmaceutical companies should adhere to the guidelines provided by FDA [77]. However, most of the results are not scientifically well-delineated hence they cannot be employed for regulatory agreements by FDA. In addition, at the time of submitting the absolute pharmacogenetic report and a truncated report, it should comply with the guidelines which have also been released associated with it [60]. Moreover, separate guidelines are there for the submission of pharmacogenetic data for investigational new drug applications and unapproved and approved marketing applications [60,64]. As mentioned above, a well-expounded pharmacogenetic test is necessary as a valid biomarker for making regulatory decisions by the FDA [19,60,64,78]. The acceptance of a pharmacogenetic test as a valid biomarker requires an articulated scientific framework and prominent characteristics [79]. Drug metabolizing enzymes [markers for drug efficacy and safety] is a good example of a valid biomarker in pharmacogenetic tests [80,81]. For instance, patients having variant alleles of the gene CYP2C9 and VKORC1 require fewer doses of warfarin, as compared to patients having normal wild-type alleles [82,83]. This is considered a valid biomarker and pharmacogenomic data has been subsumed in the drug label for warfarin [24,84–86].

6. CHALLENGES AND IMPLEMENTATION OF PHARMACOGENOMICS

Pharmacogenomic testing has been incorporated into clinical practice but at a slower pace compared to the evolving advancements in genetic research [76,87–92]. Many organizations and companies are trying to integrate and execute the pharmacogenomic testing of patients to provide them personalized therapy [93]. Some organizations have succeeded in implementing pharmacogenomics and are paving way for others. To mention a few, St. Jude hospital in the United States has been the lead hospital to implement pharmacogenomics since the 1990s [94]. They conduct Pharmacogenomics for kids' program [PG4KDS] to set up processes for using pharmacogenetic tests in the electronic health record [EHR] to preventively guide prescribing [94]. Other hospitals conduct pharmacogenomic testing of only those drugs that are prominent to adverse drug events [ADE] [20,95]. Interdisciplinary clinicians discuss the results of the pharmacogenomic test [genetic test ordered by an authorized physician before beginning the drug therapy [20,95–97].

6.1 CHALLENGES TO PHARMACOGENOMIC RESEARCH AND TESTING

Even though pharmacogenomics is anticipated to ascertain the right drug at the right dose during the pharmacotherapy by identifying individuals at risk and reducing adverse events, its appropriate use in clinical uptake, and its implementations in medical and pharmacy practice is an important issue [98,99]. Implementing pharmacogenomic testing in a clinical setting is very elusive and has to face many challenges. Some key challenges are included below:

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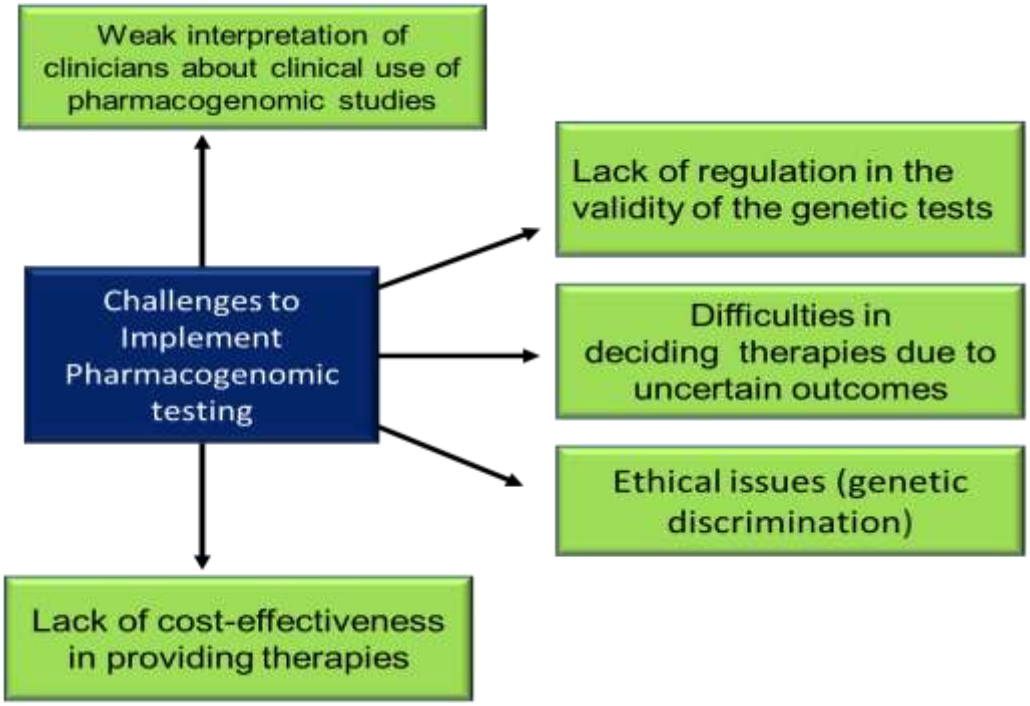

Figure 1: Challenges to implement Pharmacogenomic testing [69,76,95,98,100,101]

Clinicians should have a coherent understanding of the clinical utility of genetic testing. The application of genetic principles is used to guide therapeutic decisions [102–104]. It can be applied directly to patient outcomes by increasing the efficacy and reducing the toxic effects of the drug. Although this approach requires the creation and elaboration of guidelines that will provide substantial clarification of pharmacogenomic testing. To facilitate and implement pharmacogenomic testing for patient care and personalized therapy, we have Clinical Pharmacogenetics Implementation Consortium [CPIC] is an international association that publishes genotype-based drug guidelines assisting clinicians to understand how optimized drug therapy can be achieved using available genetic test results [105–107].

It was established in 2009 and it is an association between The Pharmacogenomics knowledge base [PharmGKB] and the Pharmacogenomics Research Network [PGRN] [106,108,109] and which alleviates complications in clinical implementation in healthcare by imparting guidelines of how to use pharmacogenomic knowledge.

6.2 CHALLENGES TO PHARMACOGENOMIC RESEARCH

Despite the potential of the conduction of pharmacogenomics research in enhancing the effectiveness development of treatment strategies for patients is encouraged, such research is a complicated and challenging task owing to the following factors mentioned in the figure. Further challenges in basic research concern a variety of additional influential factors that need to be addressed more systematically such as management & uniform representation of data, reproducibility, analysis, regulation, etc which pharmacogenomics has to overcome [89,113]. The influence of numerous non-genetic end environmental factors, including sex, age, diet, lifestyle is relevant [98]. Pharmacogenomics is on its way to executing “Personalized Medicine”. However, pharmacogenomics is facing several challenges including ethical problems in its way. If the ethical problems are not resolved and undiagnosed then the improvement and amplification of personalized medicine are very elusive. In this regard, there is various research aiming at resolving ethical issues in two fields of research and development and service provision to suggest and create some solutions [114–117].

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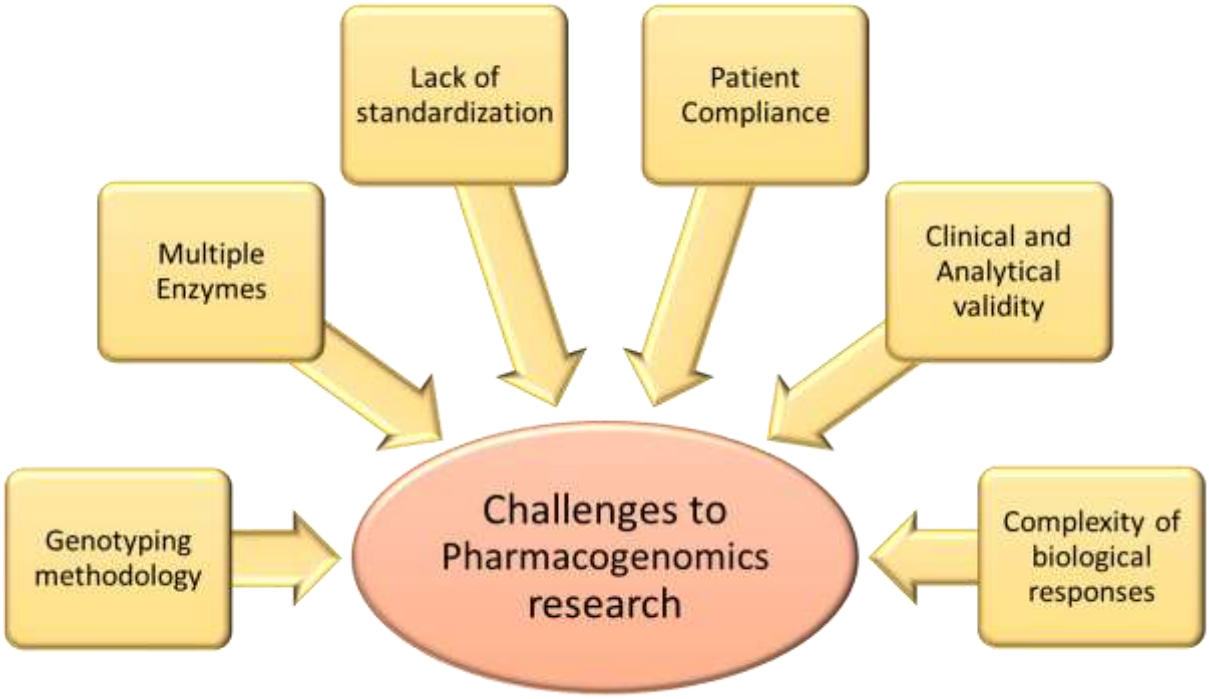

Figure 2. Challenges to implement Pharmacogenomic testing [14,110–112]

7. CONCLUSION

Pharmacogenomics in the pharmaceutical industry is a potential & promising tool, awaiting use for the maximum benefit & outcome. Currently, pharmacogenetic methods are being used worldwide, especially for assessing the safety profile of drugs. Pharmacogenomics has advanced our understanding of complex pathology, drug response, adverse drug effects, and targeted therapeutics Pharmacogenomics can facilitate the development of tailored drugs to treat a wide variety of diseases including cardiovascular disorders, cancer, asthma, AIDS. The gradual inclusion of pharmacogenomic studies in drug discovery and development will create a substantial reduction in the expenses involved in drug development, ensure a safe clinical trial and reduce failures with more accurate results. Pharmacogenomics can be implemented routinely with the help of evolving technologies and overcoming the barriers to it. The clinical implementation of pharmacogenomic research and testing ultimately depends on the robustness of cost-benefit analysis and the overall outcome and benefit of public health.

Pharmacogenomics is leading the way to develop rational means to optimize drug therapy, with respect to the patients' genotype to ensure maximum efficiency with a minimal adverse effect so that the right amount of drug is given to the right patient. It offers unprecedented opportunities to develop effective drug development and has the capacity to revolutionize patient-centric drug therapy approaches.

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