
Integrating Pharmacogenomics Into Treatments: Rationales, Current Challenges, and Future Directions

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Pharmacogenomics is a novel therapeutic concept that essentially focuses on how genes affect the body's response to different medications. Although it has the potential to revolutionize conventional clinical approaches, the actual implementations in daily practice are not as common or as easy as scientists and physicians had hoped. The disease and cancer management of patients is still very difficult due to the significant interindividual differences in the therapeutic responses observed in clinical practice. Therefore, the goal of this article is to discuss the rationales, challenges, and limitations of pharmacogenomics by analyzing several studies written by experts in diverse fields. Moreover, this article also discusses potential solutions to overcome those challenges and limitations, as well as potential future directions.

Background

The term *pharmacogenetics* was first created in 1959 by German geneticist Friedrich Vogel and has gained research attention in the field of genomic medicine in recent decades.¹ The terms *pharmacogenetics* and *pharmacogenomics* are essentially interchangeable. By studying pharmacogenomics, scientists aim to identify the influence of patients' genetic variations in response to drugs, as well as use this knowledge to design optimal therapeutic treatments based on the unique genomic profile of an individual. In addition to genetic variations among different individuals, other factors such as sex, organ function, lifestyle, and environment can all potentially explain the different drug outcomes among patients.

As Paracelsus said from a toxicology point of view, "All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison." Administering appropriate and effective dose ranges is extremely crucial when studying pharmacokinetics, which is to understand the movement of drugs in one's body. It should be noted that polymorphisms in an individual's genes can impact all parameters of pharmacokinetics including absorption, distribution, metabolism, and excretion. Thus, elucidating the mechanisms that occur during each of these parameters can give scientists insights on developing personalized medicine more holistically.

Seeing Genetics in Pharmacogenomics Through Tamoxifen

Tamoxifen is an estrogen receptor modulator that is commonly selected to treat premenopausal women with estrogen receptor-positive breast cancer. Its therapeutic effects are essentially through the metabolism of the CYP2D6

enzyme, which also has the capability of metabolizing many other drugs.² The authors listed studies that had been conducted in the past showing the strong association between CYP2D6 and the therapeutic effects of tamoxifen. Through those studies, the researchers found that individuals with much slower drug metabolism are often carrying CYP2D6*10 (c.100C>T), suggesting that various genetic predispositions could lead to different therapeutic outcomes of tamoxifen among different patients.³ This finding is significant because it can be used to further develop better therapeutic treatments by targeting the CYP2D6*10 allele. However, the authors noted that compared with the Asian population, CYP2D6*10 is extremely rare among the White population, suggesting that different racial groups have different genetic predispositions.⁴ Therefore, it is crucial to take patients' race and ethnicity into consideration when studying and developing genetic-based drugs.

Current Challenges and Limitations in Pharmacogenomics

While there is no doubt that the applications of pharmacogenomics have great potential in personalized medicine, it is important to critically examine its challenges and limitations from the standpoint of science, policy, and education.

To begin with, although the research conducted by Chan et al² on tamoxifen is significant and comprehensive in terms of conveying the importance of taking patients' race and ethnicity into consideration when studying and developing genetic-based drugs, it should be noted that they only used CYP2D6 as one of the many enzymes for therapeutic target. In reality, there are a plethora of enzymes and their corresponding isoforms that present in different racial and ethnic groups. Next, although the development of genomic technology allowed physicians to detect rare cancer mutations, different genotyping methods could occasionally miss important single nucleotides and structural variations, which in turn leads to inaccurate or false phenotype characterizations.⁵ In addition, the efficacy of drug-metabolizing enzymes can be convoluted by patients' genetic compositions, diets, use of other medications, drug metabolism rates, and even other epigenetic mechanisms, which then make the delivery of any medication at a perfect regimen with zero risks nearly impossible.⁶

There are other policy and education-based challenges of pharmacogenomics that should not be overlooked when considering its implementation. For instance, Nickola et al⁷ found that although most health care professionals believe in the merit of pharmacogenomics, they lack confidence in incorporating pharmacogenomics into prescription in their daily practices. This is due to the lack of pharmacogenomics training within their curricula, especially among health care professionals who are not pharmacists or pharmacologists.

Further, exploration into genetic mutations is currently very active and the dynamic nature of discovering genetic variations and their clinical significance creates an additional layer of complexity for pharmacogenomics research. Caudle et al⁸ stated that the lack of standardization in genomics testing and clinical laboratory processes jeopardizes the implementation of pharmacogenomics. In particular, the lack of standardization in allele function, phenotype nomenclature, and genetic variants tested subsequently leads to inconsistencies when transferring laboratory reports to the electronic health record.⁸ This in turn has complicated pharmacogenomic testing reimbursement because the pharmacogenomics community has failed to show it as readily accessible to not only health insurance companies, but also consumers. This ultimately creates additional financial burdens for patients who have to pay out of pockets if they wish to take advantage of pharmacogenomic testing as part of their medical procedures. Bielinski et al⁹ surveyed 1010 patients who previously participated in a pharmacogenomic-related study conducted by the Mayo Clinic. Upon inquiring about patients' expectations for the cost of pharmacogenomic testing, the authors found that regardless of the patients' financial status, most of them were unwilling to pay for pharmacogenomic testing and believed that their insurance companies were responsible for the full cost.⁹ The researchers found that among those who were willing to pay for pharmacogenomic testing, more than half implied that \$100 was the maximum cost they could accept.

Discussion

Finding the perfect solutions for all the challenges and limitations of pharmacogenomics will require generations of scientists to investigate and share their research with each other. However, research advancements and endeavors have made incremental progress along the way.

First, researchers have realized the importance of both pharmacokinetics and pharmacodynamics, because elucidating their roles would help identify the target genes that regulate the efficacy of different drugs. Therefore, current pharmacogenomic-based research concentrates on the idea of "genotype to phenotype." In particular, by screening candidate genes for variants, this seemingly simple approach can give scientists insights into mechanisms of drug action on single genes in various physiological pathways from a fundamental biological perspective.¹⁰ Moreover, the exploration of pathogenic single-nucleotide polymorphisms (SNPs) of different genes and enzymes that affect drug metabolism continues to expand. Scientific curators continue to review scientific literature, extract associations between SNPs and disease phenotypes, and report important information including clinical significance on databases such as ClinVar and the genome-wide association studies.¹¹ Having readily accessible and curated clinical significance of SNPs and genes can largely improve the understanding and assessment of genetic factors when designing drugs.

Second, the integration of bioinformatics in biomedical research is worth continuing because the applications of genomics and proteomics have successfully helped researchers identify predictive biomarkers as well as detect differentially expressed genes in biological samples. Such an interdisciplinary approach could also reduce the gap between biomedical research and patient-contact experience. The integration of artificial intelligence (AI) could also optimize this process. The combination of bench work, bioinformatics, and AI could efficiently analyze the patients' genetic profiles as well as predict the likely responses to certain drugs. A 2020 clinical study by Lin et al¹² found that the combination of AI algorithms, machine learning, and pharmacogenomics has leveraged their research in precision psychiatry by identifying potential biomarkers and genetic loci. They also noted that such a powerful combination has the potential to assess large-scale individual-specific clinical studies.

Educating next-generation health care professionals to ensure the better understanding of physiological processes is another valuable step toward the implementation of pharmacogenomics. Nickola et al⁷ described an exemplary case in which students at the Bernard J. Dunn School of Pharmacy at Shenandoah University were exposed to profound pharmacology, biostatistics, and genetics-related courses by participating in a joint baccalaureate program with the George Washington University School of Medicine during their first 2 years of enrollment. This core curricula provide unique hands-on opportunities for students where they can engage in anonymous genotyping exercises as well as reinforce their knowledge and experience by writing a thesis paper at the end of the program. It should be noted that changing the curricula by integrating pharmacogenomic-related knowledge and skills is not going to be an immediate fix, because building a firm knowledge foundation requires many factors and components to coordinate well together in the long-term. However, Nickola et al⁷ observed positive outcomes as evidenced in the increased level of interest and confidence with pharmacogenomic-related concepts among those students.

Last but not least, the use of electronic health records and standardization of genetic variant nomenclature have improved the lack of standardization issue in clinical laboratory and genetic testing. Experts from prominent institutions and consortiums, such as American College of Medical Genetics, Clinical Pharmacogenetics Implementation Consortium, and Human Genome Variation Society, are working to establish a more unified translation that can minimize the misunderstanding and confusion regarding genotype to phenotype.⁸ Furthermore, more specific and reimbursable *Current Procedural Terminology* codes are constantly being developed to ensure the result reporting process goes more smoothly, which would potentially lead to greater and more consistent reimbursement in the future.

Future Directions

Moving forward, having efficient collaboration between health care professionals and scientists is essential because each one of them has their unique trainings and specialized expertise. Those experts may view and tackle the same problem differently, which in turn allows them to contribute to the field of genomic medicine distinctively. For example, a physician may not understand the raw data generated from pharmacogenomic-testing without the help of a bioinformatician. Thus, experts in different fields should consider collaborating and translating their work and significance to the next recipient of the health care network to avoid any misinterpretation and misunderstanding when working with patients.

Moreover, once the structure and techniques of pharmacogenomics become more developed and mature in the future, government could make pharmacogenomic testing part of publicly funded health care. As of right now, pharmacogenomic-oriented diagnosis and therapeutic treatments are only granted to those who can afford and have access to it, which creates additional health care disparities. On the other hand, informing and educating the general public on pharmacogenomics in a way that does not make pharmacogenomics sound too overpromising is not trivial. This is because the field is still being gradually explored and there are more unknowns than knowns to unravel in the future.

Finally, from the tamoxifen study conducted by Chan et al² to the lack of standardization discussed by Caudle et al,⁸ the observations and conclusions were all made within a relatively narrow region, that is, in a single country. Different countries have different standards and perspectives on incorporating pharmacogenomics into clinical practice. For example, to accelerate the implementation of pharmacogenomics into clinical practice, the European Commission has launched the Ubiquitous Pharmacogenomics (U-PGx) Consortium with a unique preemptive approach, which in a stepwise manner begins from developing pharmacogenomics tools to educating physicians to apply pharmacogenomics during routine care.¹³ Hence, it is worthwhile to learn from other countries' approaches and strategies by having international summits or panel discussions.

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