Evaluating the Clinical Utility of Genetic Testing in Guiding Medication Selection

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Abstract

The study of genetic factors influencing medication response variability is known as pharmacogenetics. Pre-emptive genotyping of germline pharmacogenetic variations by personalised medicine programs indicates a growing interest in using clinical pharmacogenetic testing. Pharmacogenomics, a flourishing branch of pharmacy, establishes to initiate the use of individual's personalized genetic information's to guide treatment therapy. Pharmacogenetics reveals that SNPs in candidate genes are directly associated with efficacy and/or toxicity of prescribed drugs However, obstacles like as cost, integration into clinical practice, and the need for more education among healthcare personnel remain. Pharmacogenomics has the potential to significantly improve personalised medicine as it becomes more widely used, which will increase patient care.

Keywords: Genetic Testing, Drug Therapy, Pharmacogenomics, Adverse Drug Reactions.

1 INTRODUCTION

The National Institutes of Health (NIH) in the United States defines genetic testing as the analysis of human chromosomes, genes, or proteins with the aim of detecting heritable illnesses in clinical settings. For many years, prenatal screening, carrier screening for genetic disorders intended for reproduction, and diagnosis of uncommon Mendelian disorders suspected based on clinical evidence or family history have all involved genetic testing (National Academies of Sciences). Now that high-throughput genomics has advanced, large-scale genotyping and sequencing can be affordably done. As a result, more genetic tests are being created, including direct-to-consumer genetic testing that are sold commercially and tests intended for clinical use. Genetic testing is suggested as a way to direct medication therapy to enhance medicine efficacy or prevent side effects in the developing discipline of pharmacogenomics. Nonetheless, there are still a number of obstacles that prevent genetic data from being widely used in the clinical care context (Malsagova et al., 2020; Katz & Schweitzer, 2010).

By elucidating suitable treatments for certain disease subtypes, pharmacogenomic and pharmacogenetic testing—which detect genetic variants that may aid in predicting therapeutic efficacy

and/or toxicity—contribute significantly to the field of precision medicine (Malathi et al., 2024). Since there may be terminological variations depending on whether drug-gene interactions or drug responses from many genes are being discussed, we shall refer to both pharmacogenomic and pharmacogenetic techniques in this review by the acronym PGx. Genetic testing has been shown to be particularly beneficial for individuals on anticoagulants such as warfarin. Variations affecting the CYP2C9 and VKORC1 genes have a significant effect on warfarin metabolism. It has been shown that pharmacogenomic-guided dosing reduces side effects like thrombosis and bleeding.

Numerous medical conditions can now be tested for with PGx, including infectious diseases, autoimmune disorders, cancer, diabetes, heart disease, and mental health issues (Neelima et al., 2024). Patients are presently experiencing real benefits on a daily basis, such as better outcomes and lower overall health care expenses (Sonya & Kavitha, 2022). Nevertheless, there are numerous obstacles in the way of PGx-guided therapy's complete adoption by patients, payers, and practitioners as well as its complete integration into clinical practice. Genetic testing has also been proposed as a way to reduce the risk of major side effects associated with statins, which are among the most often prescribed drugs and typically safe and well tolerated (almost 50% of persons 65 years and older have a prescription for a statin). The most frequent adverse effect is myopathy, which can cause acute kidney injury, muscular damage, and potentially fatal rhabdomyolysis. Mild myalgias might not cause any medical harm, but they can make patients less likely to stick to their statin treatment regimen (Mansouri, 2023). In clinical trials, the incidence of statin-associated myopathy ranges from 1 to 5%; in clinical practice, however, the incidence is higher. The risk of statin-induced myopathy is heritable, and the significance of PGx testing in directing the pharmacotherapy of statins is changing, especially with regard to the gene encoding the solute carrier organic anion transporter family, member 1B1 (SLCO1B1). Most payers do not cover routine PGx testing for statin medication, and current guidelines do not advocate it (Hudson, 2006).

2 LITERATURE REVIEW

According to a meta-analysis (Mega et al., 2010), carriers of the CYP2C19 loss-of-function allele had an increased risk of cardiovascular death, myocardial infarction, or stroke when treated with clopidogrel compared to non-carriers. There are significant differences in antidepressant efficacy and tolerance. The optimal usage of medications such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) is facilitated by genetic testing for enzymes such as CYP2D6 and CYP2C19 (Koopmans et al., 2021). Individuals who have ultra-rapid or poor metaboliser phenotypes are more susceptible to unpleasant reactions or non-reactions.

A study (Pirmohamed et al., 2013) shown that genetic testing for warfarin dose lowered the occurrence of severe bleeding.

According to a study, individuals getting pharmacogenetically guided treatment for depression showed better remission rates and quicker response times than those on standard care.

Collins, (1999) asserts that genetic testing ought to be a regular part of medical care, particularly in the case of early diagnosis and illness prevention (Uyan, 2022). Clinical validity-related worries Critics such as warn that although genetic testing has great potential, the intricacy of gene-environment interactions limits the therapeutic value of many tests for multifactorial disorders. Healthcare administrations, they contend, ought to prioritise tests that have demonstrated efficacy (Alamer et al., 2023).

In uncommon illnesses (Boycott et al., 2017) promote genetic testing as a significant advancement in the diagnosis of uncommon disorders, offering comfort to families who have long suffered from unidentified illnesses. This viewpoint emphasises how crucial genetic testing is to providing individualised treatment plans. The study that establishes a connection between genetic variation and clinically significant medication responses is known as pharmacogenetics (Malešević et al., 2023). It sought to reduce hazards and increase the advantages of medication treatment. According to (Pirmohamed et al., 2013), there may be an improvement in patient safety if genotype data is integrated with medicine dosage. Research teams studying pharmacogenetics have discovered the genetic underpinnings of differences in medication toxicity, dose requirements, and efficacy. Pharmacogenetic data have improved our understanding of many medications' metabolism and mechanisms of action, as well as developing prospective clinical uses (Johnson, 2003).

With the use of pharmacogenetics, a patient's dose and medication combination can be determined that will most likely be safe, effective, and provide a therapeutic response without causing an unfavourable drug reaction. Freidrich Vogel, at Heidelberg, Germany coined the term pharmacogenetics in 1959. Nonetheless, Sir Archibald Garrod established the field much earlier, in or around 1898, when he was interested in researching urine pigments in alkaptonuria patients. Garrod, with remarkable insight, was the first to propose the idea of chemical individuality.

Pharmacogenetics include unfavourable drug responses involving excessive drug response, contact with an incorrect target, or an abnormal immunological response to the treatment in addition to variations in drug metabolism and drug targets. Primidone, a medication used to treat malaria, and isoniazid, a treatment for tuberculosis, were among the first medications whose metabolising enzymes had genetically determined differences that resulted in side effects.

Among genetic variations, single nucleotide polymorphisms (SNPs) are the most prevalent. In the DNA sequence, it is a single base pair that has changed. However, SNPs can result in functional alterations through altering transcription factor binding affinity, mRNA transcript stability, and amino acid composition. It is anticipated that SNPs would facilitate the faster discovery of genes responsible for diseases by enabling researchers to explore for correlations between an illness and certain sequence differences (SNPs) within a group of people. These association studies are not the same as the more common method of tracking a disease's transmission within a family, known as pedigree analysis. Because it is far easier to get DNA samples from a random selection of persons in a population than it

is to obtain them from every member of a family over several generations, association studies should hasten the Discovery of disease genes (Syvänen, 2001).

Haplotype mapping is another application for SNPs, where a single SNP can be used to find connected SNPs for sites where alleles are crowded together. Even though the loci may not be on the same chromosome, Linkage Disequilibrium (LD) denotes a non-random linkage of alleles at two or more loci. This indicates that DNA sequences and SNP alleles that are closely spaced out in the genome are more likely to be inherited together. As a result, LD will decrease with increasing SNP distance. Conversely, an increased recombination rate results in an increased LD.

In order to facilitate the identification of the numerous genetic risk factors for diseases that are frequently observed in the population, Genome Wide Association Studies (GWAS) examine variations in DNA sequence throughout the human genome. Utilising these genetic risk variables to forecast who in the population is more vulnerable is the primary goal of GWAS. These predictions will aid in understanding the numerous elements involved in the particular illness susceptibility so that newer preventive and treatment measures can be devised. The field of pharmacogenetics is one of the most significant uses of GWAS. Pharmacogenetics facilitates the discovery of DNA sequence variants linked to pharmacological efficacy, metabolism, and side effects (Malešević et al., 2023).

2.1. Types of Genetic Testing

There are many different types of genetic tests available. These include single-variant tests (e.g., diagnosis of the HBB p.Glu7Val mutation [a substitution of valine for glutamine at amino acid 7 of beta globin] that causes sickle cell disease], gene-based tests (single or multiple genes, such as genetic testing for autosomal dominant polycystic kidney disease [ADPKD] mutations in the PKD1 and PKD2 genes), and genetic panels (e.g., for genetic variants associated with drug metabolism). Genetic testing cover variants in single nucleotides, haplotypes (such the HLA region), copy number variations, deletion/insertion variants, and mutations in mitochondrial DNA. Whole-exome and whole-genome sequencing use next-generation sequencing (NGS) techniques for high-throughput DNA analysis to identify Mendelian disorders when clinical features and family history suggest a genetic aetiology (Uffelmann et al., 2021).

The most affordable approach to genetic clinical diagnosis may involve combining whole-exome sequencing with Sanger sequencing to validate relevant genetic variants when multiple loci can explain a specific illness. Nonetheless, it is uncertain if patients would obtain data for mutations for which the clinical significance has not yet been established (variants of unknown significance, or VUS) (Crossley et al., 2020). For forecasting sickness risk in individuals without a known genetic problem, direct-to-consumer offerings include whole-genome sequencing and genome-wide genotyping arrays. The clinical use of these tests in healthy individuals without symptoms is questionable, and there may be detrimental consequences from revealing unintentional results and/or genetic abnormalities, such VUS, for which there is no recognised clinical significance (Bobir et al., 2024).

2.2. Genetic Test Validity and Utility

A test's clinical validity is determined by the evidence linking the variant to a particular disease. Functional details regarding the variant under investigation are included in this evidence, such as the possibility that loss of function mutations—which damage the ability of genes that code for proteins—will impact phenotypes or cause a medical condition. Nonetheless, it is unknown how many variations work (Burke, 2004).

The proof that the test enhances clinical outcomes and, thus, supports patient treatment choices is known as clinical utility. For instance, randomised clinical trials have not produced enough data to support the therapeutic value of the majority of examined variations (Mohandas et al., 2024).

2.3. Genetic Testing to Guide Drug Choice

By determining a patient's susceptibility or resistance to medications used to treat their ailment, genetic testing can aid in treatment choices (drug efficacy) (Filipski et al., 2016). For instance, the FDA-approved medication ivacaftor controls the function of the transmembrane conductance regulator (CFTR) channel in cystic fibrosis. Eighty-five to ninety percent of people with cystic fibrosis who are of European ancestry contain at least one copy of the functional variation F508del, which results in an aberrant CFTR protein. Additional variations linked to the drug's ineffectiveness and variations linked to its lack of reaction.

2.4. Genetic Testing to Direct Medication Dosage

Genetic variants can impact how medications are metabolised (pharmacokinetics), which can aid with dose changes to prevent overexposure to pharmaceuticals or undertreatment. For example, there is considerable inter-individual variation in the dosage of the oral anticoagulant warfarin needed to achieve the therapeutic range, which can be attributed to both hereditary and dietary factors. A common medication used to treat and prevent thromboembolic disorders is warfarin. Warfarin has a restricted therapeutic range, and there may be dangers associated with increased or decreased international normalised ratios (INRs). To determine the appropriate warfarin dosage, CPIC currently advises testing for genetic variants in the target enzyme for warfarin action, in genes related to warfarin metabolism, and in pathways related to vitamin K recycling.

2.5. Pharmacogenetics

Given that genes influence how the body reacts to medications, genetic testing may be used to guide treatment strategies, such as preventing side effects and other serious issues. With the information that genetic testing may provide on treatment effectiveness (e.g., non-responders) and impacts on drug metabolism (faster versus slower metabolisers), tailored therapeutic dosage may be achievable. Furthermore, pharmacogenetic testing can be employed to determine which individuals are most likely to experience severe idiosyncratic adverse events. This information can then be used to inform medical decisions on medication selection and the adoption of alternative treatment approaches. Despite the

increased interest in pharmacogenetics, there is still a significant knowledge vacuum about useful variations (Johnson, 2003). Pharmacogenomics and Drug Response in Individuals with Different Genotypes Shown in Figure 1.

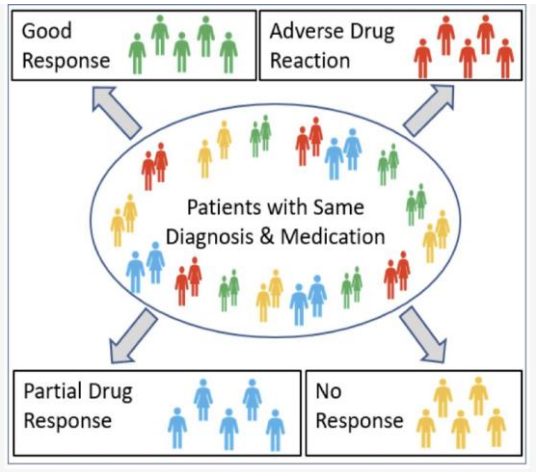

Figure 1: Pharmacogenomics and Drug Response in Individuals with Different Genotypes

3 PROBLEMS AND RESTRICTIONS WITH GENETIC TESTING

The lack of clinical validity and utility for some genetic variants (such as most variants found in genome-wide association studies) and the availability of less expensive alternatives (such as dosing blood levels of the medication rather than adjusting based on genetic testing) are some of the obstacles to the widespread use of genetic testing for patient diagnosis and treatment. Efforts should focus on educating healthcare professionals about test availability, interpretation, and recommended therapeutic interventions based on test results in order to enhance their access to information about a limited number of variants, primarily in pharmacogenomics, that have strong evidence for preemptive screening. Genetic-driven clinical treatment decisions will be made easier by integrating genetic testing into electronic medical records (Katz & Schweitzer, 2010). Chart Shows the Size of Global Direct - to - Consumer Genetic Testing Market (2014- 2022) shown in Figure 2.

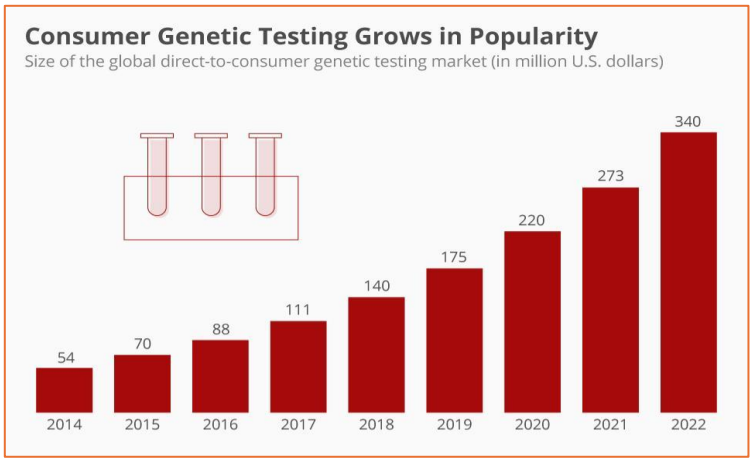

Figure 2: Chart Shows the Size of Global Direct - to - Consumer Genetic Testing Market (2014- 2022)

Numerous genes influence most diseases or features, including chronic kidney disease (CKD), which is polygenic. This is why multiplex genetic panel testing may be more advantageous for pharmacogenomics and the detection and diagnosis of genetic disorders. Genetic testing will likely be more economical if it focusses on members of a racial or ethnic group where the variant is more common, as the frequency of variants varies among ancestral populations and some variants may be uncommon in particular ethnic groups.

Numerous interesting directions for future research are presented by the clinical value of genetic testing in directing prescription selection. One major possibility is to further our understanding of pharmacogenomics through population-based, large-scale research including a variety of racial and demographic groups. This will assist in identifying genetic variations that affect drug efficacy, safety, and metabolism in different populations. Furthermore, further research is required to develop strong clinical guidelines that integrate genetic testing into standard practice, particularly for drugs with limited therapeutic windows or high patient response variability. Interdisciplinary cooperation involving geneticists, physicians, and bioinformaticians are crucial to improving the application of pharmacogenetic testing. African-American folks today face unique hurdles when undergoing genetic testing. A comparison between the occurrence of a variation in sick and unaffected individuals is crucial in assessing its pathogenicity. Finding a VUS is far more likely in Africa due to the large genetic variety of the continent and the dearth of data from normal individuals. It is imperative that diagnostic laboratories work together to create national data resources, save data, and share variants in order to maximise interpretation throughout the African continent.

4 RESEARCH OPPORTUNITIES AND RECOMMENDATIONS

Inter-individual heterogeneity in drug response—whether it be safety or efficacy—is prevalent and is expected to worsen worldwide as the number of elderly people needing treatment rises. Pharmacogenomics, a field of study, has identified genetic variables as one of the causes of this inter-individual heterogeneity. Many countries throughout the world are currently focussing on adopting pharmacogenomics into clinical practice, which is commonly regarded as one of the first steps in mainstreaming genomic medicine. This is because genotyping technologies are becoming more and more accessible and affordable. The alteration of current clinical pathways and a significant knowledge gap in pharmacogenomics among the medical workforce provide significant implementation issues for health-care systems. With mounting data indicating that targets that are determined by DNA have a higher chance of success in clinical trials, pharmacogenomics can also be applied more broadly to drug research and development. It goes without saying that pharmacogenomics is still a new field that will grow over the coming years. The potential benefits of pharmacogenomics in clinical care are limited by our current poor understanding of the genetic influence on drug reactions. By expanding the number of uncommon variants linked to medication response and applying systems pharmacology techniques, we might improve our comprehension of pharmacogenomics and consequently, the advantages and

significance of this field of study. In order to accomplish this, the U-PGx consortium will employ two strategies: (1) employing Whole Genome Sequencing (WGS) to detect uncommon variants linked to drug response, and (2) utilising systems pharmacology models that incorporate various variables like co-medication, gender, and age to identify and clarify drug-drug-gene interactions. When it comes to pharmacogenomic-guided prescribing and dispensing, the adoption of WGS might not be the most economical strategy at this time. Still, as time goes on, the cost of this technique will asymptotically approach a threshold where whole genome sequencing (WGS) will no longer be driven by cost but by technology when applied to pharmacogenomics. Because each statin has a different pharmacokinetic profile, more research is required to assess the therapeutic relevance and cost-effectiveness of PGx testing in specific patient populations. Other criteria to consider include the type of statin being used, its dosage, and any concurrent medication use.

5 CONCLUSION

Pharmacogenomics holds the possibility of personalised treatment, whereby the genetic makeup of each patient would help in medicine selection and dosage determination. This is in contrast to the existing empirical approach, which depends on the doctor's knowledge of therapeutic options as well as dosage data based on body weight, age, and, if relevant, renal clearance. The ultimate goal is to significantly lower the frequency of adverse medication reactions and boost therapeutic responsiveness through the use of pharmacogenomics in clinical practice.

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