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The Role of Pharmacogenomic Testing in Tailoring Medication Therapy to Individual Patients

Omar Shaffay Alenzy[1], Abdulaziz Abdullah S AlOtaibi[2]

[1] Corresponding Author, Pharmacist, Omarshaffai57@hotmail.com,

[2] Pharmacist in king Abdelaziz medical city, Rewesa@ngha.med.sa

Abstract

Pharmacogenomics refers to the study of how an individual's genes can affect their response to medications and emerges from the broader fields of pharmacology and genomics (Barone et al., 2009). Because each patient's genetic make-up is unique, they will respond differently to the same medication. Some patients may find a medication effective, while others may find it ineffective, and still others may suffer adverse side effects. Pharmacogenomics seeks to develop a new generation of medications that will be tailored to individuals, thereby reducing the guesswork in prescribing medications. Many medications currently prescribed have been developed without consideration of how an individual's genetic make-up might affect their response (Tucker, 2008). Individually tailored medications are expected to be the ultimate goal of pharmacogenomics; however, even partially successful efforts would have a significant impact on health care in the United States.

As an alternative to health care costs rising, pharmacogenomics could mean that health care dollars go significantly farther by spending less on each individual patient. One promising new technology is pharmacogenomic testing: genetic assays that can be performed on a patient's DNA to guide their drug therapy. These tests can help physicians select the most effective medications for their patients while avoiding medications that can cause serious side effects. There has been a plethora of pharmacogenomic research for many different drug classes, and there are already pharmacogenomic tests commercially available. These pharmacogenomic tests could be performed as part of a patient's routine medical work-up: to guide drug selection for patients prior to starting therapy, ensuring the best possible medication is prescribed from the beginning. A new class of medications that are effective but have a high risk of side effects could benefit greatly from pharmacogenomic testing.

Keywords: Pharmacogenomics, Personalized Medicine, Genotyping, Drug Therapy, Individual Patients, Healthcare System.

1. Introduction to Pharmacogenomics

Pharmacogenomics, the integration of pharmacology and genomics, is the study of how a patient's genes could affect their response to a drug. Essentially, it is a way to personalize medicine and prescribe the optimal drug at the most advantageous dose for that patient

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(Barone et al., 2009). In simpler terms, pharmacogenomics is the consideration of a patient's genetics when deciding what medications to prescribe. The field of pharmacogenomics is mainly focused on adverse drug reactions, which are unintended and harmful responses to a drug. Almost all drugs can cause some sort of reaction, and the severity of which can range anywhere from a minor inconvenience to death. Adverse drug reactions are a major problem with currently prescribed medications. There are approximately 2 million serious drug-related events annually in the United States, leading to over 100,000 deaths. Because of the complexity of the human body and the numerous variables involved, no drug is perfectly safe. Even so, the risk of an adverse reaction to a drug can be greatly reduced by selecting a drug that is the most effective for that patient, and pharmacogenomics could lead to that possibility.

For centuries, physicians have prescribed the same drugs to all patients with the same disease. One medication can be effective for one patient, but have little effect on another. For example, paroxetine is a commonly prescribed antidepressant. In one study, 60% of patients currently taking paroxetine were found to be non-responders to the drug, meaning the drug had no effect on their depression (Tucker, 2008). There can be substantial variation in response to a medication among patients, even though they exhibit similar symptoms or diagnoses. One explanation for this phenomenon is genetic variation. A single nucleotide polymorphism (SNP) is a difference in a DNA building block, called a nucleotide, that occurs at a particular spot in the genome. SNPs are the most common type of genetic variation and can affect how individuals respond to certain drugs. For this reason, pharmacogenomic studies are emerging across all aspects of medicine.

1.1. Definition and Scope

Pharmacogenomics (PGx) is the study of how genes affect a person's response to drugs. PGx testing can help determine how individual patients may respond to specific medications, and therefore can be used to assist in selecting and personalizing medications. The use of PGx testing has been steadily growing across the nation. Focused, targeted initiatives that highlight the value of incorporating PGx testing into clinical practice may further enhance PGx use within healthcare systems (W. Guy et al., 2020).

Pharmacogenomic testing uses a patient's unique genetic makeup to determine how they will respond to certain medications, and therefore can help to select the best medication for a patient. Medications with known pharmacogenomic considerations have been found across multiple therapeutic areas, including psychiatry, cardiology, oncology, pain management, and infectious diseases. Starting with the clinical implementation of pharmacogenomic testing in psychiatry, this assessment reviews the current applications of pharmacogenomic testing across therapeutic classes and the medications with the most robust clinical evidence supporting the use of pharmacogenomic testing.

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1.2. Historical Background

Prior to the mapping of the human genome, there was evidence that genetics could affect drug response. Earlier studies had reported that patients with reduced prodrugs clopidogrel and azathioprine activation, which could be due to the presence of the inactivated alleles of the hepatic CYP2C19 and NAT2 enzymes correspondingly, had the higher risk of adverse clinical outcomes following the coronary stenting and inflammatory bowel disease's surgery (HN van Schaik, 2014). In 2010, the US FDA proposed to consider providing guidelines for the use of antidepressant citalopram, a 2D6 substrate, in patients with the 2D6 gene multiplicity or deletion, due to the possibility of drug-induced QTC prolongation and Torsade de pointes. In 2012, the FDA amended the label of the 2D6-metabolized opioid codeine, requiring to assess the 2D6 genotype prior to prescription in pediatric patients to exclude ultra-rapid metabolizers, at a risk of life-threatening respiratory depression. The concept of pharmacogenetic testing in clinical routine was demonstrated in the previously treated with 6-mercaptopurine pediatric patients with acute lymphoblastic leukemia. Drug sensitivity was shown to be determined by the presence of the inactivated alleles of the thiopurine S-methyltransferase (TPMT) enzyme, leading to a recommendation to jointly assess the TPMT genotype prior to treatment initiation. Recent studies have demonstrated that the CYP2D6 status could affect the risk of Torsade de pointes in patients treated with psychiatric drugs.

Pharmacogenomic testing has advanced beyond the experimental stage and is recognized as the practice of using a patient's genetic information to optimize drug therapy. The initial perception problem – the terminology's multiplicity – has mitigated in part thanks to the widespread adoption of "pharmacogenomics". Nevertheless, there are still discrepancies in the interpretation of the term "clinical application of pharmacogenomics". There is uncertainty whether this is the laboratory component only, or pharmacogenomics includes also a responsibility for the test results interpretation. The interpretation responsibility is critical, since the complexity of the results interpretation stems primarily from the diversity of the testable genes and drugs combinations. Currently, there are genes with the well-defined action mechanism, yet different drugs could interact with the same target protein. There are drugs that act on multiple targets and thus involve several genes. Conversely, a single gene could affect the action of various drugs and have different phenotypic consequences. Finally, a particular drug disposition's and action's diversity-inducing gene could have different polymorphisms across the ethnic populations.

2. Principles of Pharmacogenomics

Pharmacogenomics is the study of how genes affect a person's response to drugs. This is a subgroup of pharmacogenetics, which focuses on single gene effects. By combining pharmacology and genomics, this study aims to develop effective, safe medications and doses that will be tailored to the patient's genetic makeup. Variations in genes that code for drug

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metabolizing enzymes, drug transporters, drug receptors, and drug targets can affect individual responses to different medications including over-the-counter drugs, prescribed medications, and herbal therapies (HN van Schaik, 2014). Variations in such genes can lead to toxicity, ineffective therapy, or a therapeutic effect. With the advancements in genomic technologies and the resultant decrease in costs, pharmacogenomics has changed the landscape of drug therapy for several disease states including cardiovascular diseases, cancer, mental illnesses, epilepsy, infectious diseases, and many others (Elewa & Awaisu, 2019). Genome-wide association studies (GWAS) have identified several pharmacogenomic loci linked to monogenic and polygenic diseases. The application of pharmacogenomics in clinical practice has resulted in improving the efficacy and minimizing the untoward effects of several drugs. At the same time, a number of drugs have failed in clinical trials and some have been withdrawn from the market due to toxicity that has led to unexpected adverse effects and deaths. To address these issues, the FDA has recommended the inclusion of pharmacogenomic studies during the clinical development of new drugs. Efforts are also being made to incorporate pharmacogenomics in the preclinical stages of drug development. Several clinical and neighborhood studies have highlighted the clinical implications of pharmacogenomics in different disease states. Despite the advancements in pharmacogenomic applications, many studies have highlighted the gaps and difficulties in implementation.

2.1. Genetic Variability in Drug Response

Genetic variability among individuals may account for differences in drug effectiveness, toxicity, and the ability to metabolize drugs (Barone et al., 2009). Additionally, environmental factors such as diet, lifestyle, and other external factors can also affect an individual's pharmacogenomic profile. Treatments that are effective in the majority of patients may not work effectively for everyone. The field of pharmacogenomics studies the role of genes in determining an individual's response to drugs. Drugs with high variability in response among individuals would be prime candidates for pharmacogenomic studies. Because of their high use and the high degree of variability among patients, cardiovascular drugs are the focus of many ongoing pharmacogenomic studies. Currently there is evidence that genetics partially account for variability in drug response. Researchers have focused on single-nucleotide polymorphisms (SNPs) and DNA copy number variants (CNVs). Pharmacogenomic studies are aimed at linking SNPs or CNVs to how individual patients respond to a particular medication.

2.2. Drug Metabolism Pathways

Pharmacogenomic (PGx) testing can optimize drug therapy by determining whether an individual possesses specific genetic variants that impact drug efficacy or toxicity. Genotype-guided drug prescription based on FDA drug labels with PGx information has been shown to

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affect drug therapy outcomes. Various studies have examined the effect of pre-emptive PGx testing on different patient cohorts. For example, a study in the Netherlands found that anesthetized patients undergoing surgery with pre-emptive PGx testing had a shorter time to optimal drug dosing compared to those not tested (HB Wu, 2011). Another study with psychiatric patients reported fewer adverse drug reactions after PGx testing. In emergency departments, testing for 12 relevant PGx variants was found to be feasible and clinically applicable. A cohort study in Spain with heart patients demonstrated that cardiology physician adherence to PGx test results changed drug prescriptions in 67% of cases, with higher rates for pre-determined tests and direct referrals.

Drugs have a wide range of bioactivity and toxicity due to their unique mechanisms of action and chemical structures. A drug's biological fate is dictated by its pharmacokinetic (PK) and pharmacodynamic (PD) properties. Drug metabolism is a critical component of pharmacokinetics and is subject to genetic variations in drug metabolizing enzymes (DME). Polymorphic DME activity can lead to altered therapeutic efficacy or unexpected toxicity, resulting in adverse drug reactions (ADRs), the leading cause of drug attrition during clinical trials and critical safety issues post-marketing. Pharmacogenomics is the study of how an individual's genome affects their response to drugs. Genotyping key DMEs can minimize the risks and improve the chances of success for drug therapy.

3. Clinical Applications of Pharmacogenomic Testing

Emerging pharmacogenomic applications that are clinically available and clinically validated largely revolve around psychiatric medications, cardiovascular medications, pain management, and autoimmune medications. Clinical pharmacogenomic testing has the potential to substantially reduce healthcare costs due to the optimization of drug therapy choices. During the first year of implementation, pharmacogenomic testing of 674 patients in a health system avoided $1,370,658 in treatment costs attributed to prolonged hospital stays and admissions to the emergency department (HN van Schaik, 2014). Clinical pharmacogenomic testing for CYP2C19 genotyping has been shown to be economically beneficial for patients undergoing percutaneous coronary intervention with the evaluation of clopidogrel response.

Out of 218 eligible patients, those tested and retained in an informed consent pathway were more likely to be treated with a compatible antiplatelet therapy post-discharge compared to non-tested patients. This resulted in fewer readmissions due to acute coronary syndrome ($p=0.050$), as well as approximately $76,491 in estimated savings for the health system. Utilizing pharmacogenomic testing to guide the treatment of hyperlipidemia from statins may also be economically feasible with a negligible cost of $30 for a valid PGx test policy for a patient, resulting in cost savings via the avoidance of the selection of inappropriate therapy ($344 per patient).

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3.1. Drug Selection and Dosing

Pharmacogenomic (PGx) testing analyzes variations in DNA sequence and gene expression to assess drug efficacy in individual patients. With PGx testing, healthcare providers receive unique genomic data that can be used to customize therapeutic drug dosage and selection, thereby avoiding the administration of ineffective medications. Drug selection and dosing is the most researched clinical application of pharmacogenomics (de Leon, 2009). It accounts for 92 currently available PGx tests across 20 different genes and 36 FDA-approved drugs. Implementation of most currently available PGx tests is feasible, as they examine one or two genes and can be performed on a blood sample. Each test would provide a unique genomic measurement for a healthcare provider, who could then customize a patient's drug selection and dosage. Physicians presently have access to numerous drugs for the treatment of a single disease. For example, there are twelve different drugs for the treatment of HIV-1, ten drugs for the treatment of hepatitis C virus, and more than 140 drugs for the treatment of various cancers. Beyond drug access, physicians also have access to specific biomedical measurements that can be used for drug selection in patients. For instance, the HIV-1 protease activity can be measured to assist the selection of a protease inhibitor for HIV-1 infected patients, as can a patient's genotype of the hepatitis C virus for selecting an antiviral treatment. However, in the vast majority of situations, patients receive no specific measurement to assist drug selection or dosing in their unique context. Hence, a consideration of efficacy in a "trial-and-error" manner becomes essential.

3.2. Adverse Drug Reactions Prediction

Adverse drug reactions (ADRs) not only constitute a major burden for affected individuals but also for the health care system in general. ADRs are one of the most common causes of hospitalization, increased length of stay, and death of patients. Furthermore, ADRs result in excess costs due to up-scaling treatment strategies, diagnostic costs, and non-productive time of health care professionals (Böhm & Cascorbi, 2016). ADRs are often of multifactorial origin, but patient-specific factors, including genetics, immune status and co-medication, play a crucial role (H. Thabet et al., 2023). Among these factors, pharmacogenetic variations are able to change the pharmacokinetics and/or pharmacodynamics of a drug or its active metabolites, thereby influencing drug efficacy and safety.

Pharmacogenomic testing has the potential to broadly change the treatment and prevention of ADRs. While the majority of ADRs are not caused by changes in drug pharmacokinetics and are therefore classified as "pharmacological ADRs", population studies have shown that patient genotypes alone can contribute to an increase in interindividual variability of a drug's efficacy and toxicity. For some drugs, this pharmacogenomic effect was larger than the drug dose effect. The other strategies to avoid ADRs include avoidance of specific drugs, changed routes of application, co-medication, and use of alternative drugs. Pharmacogenetic testing is

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able to directly predict several types of drug ADRs prior to drug application, especially drug hypersensitivity reactions.

4. Technological Advances in Pharmacogenomics

Pharmacogenomics relies upon new scientific advances and innovation to demonstrate clinical utility. Several new technologies have emerged and streamlined the scientific process for pharmacogenomics. FilmArray provides a rapid and accurate means of achieving genotyping and is the ideal starting point for pharmacogenomic test development. Secondary research into bioinformatics pipelines demonstrated alternative methods of achieving findings that are similar to those achieved via commercial software. These alternative methods make screening for pharmacogenomic variants achievable in any lab setting, regardless of financial resources. Finally, research into user interface design has shown that the implementation of a simple interface will greatly assist non-technical individuals in interpreting pharmacogenomic results ((Gouri) Mukerjee et al., 2018). The combination of these new technologies expands the potential for pharmacogenomics to be integrated into clinical practice.

Clinical pharmacogenomic testing currently comprises a single, small panel that consists of six genes. This limited test was developed as a proof-of-principle for pharmacogenomic testing to demonstrate that it is both affordable and achievable in a community hospital setting. Testing for additional and larger panels of pharmacogenomic variants is both achievable and reproducible; however, further community and provider investment in biobanking will be required. Community hospitals are also encouraged to pursue partnerships with academic institutions that run commercial pharmacogenomic panels. These partnerships present unique opportunities to achieve the ideal standard-of-care for pharmacogenomic testing (HN van Schaik, 2014).

4.1. Next-Generation Sequencing

In recent years, next-generation sequencing (NGS) technologies have become widely available and cost-effective. NGS has been used in clinical laboratories for the diagnosis of a variety of diseases and is becoming an integral component of personalized medicine. Pharmacogenomic (PGx) testing can deliver significant clinical benefits, preventing adverse drug reactions (ADRs) and treatment failures, and improving drug efficiency. While most current PGx tests rely on single gene Sanger sequencing or other genotyping methods, the focus in the near future will be on the implementation of NGS technologies. Here, the clinical PGx workflow is summarized and the role of NGS is discussed at each step. Pathogenicity interpretation of pharmacogenomic variants will greatly benefit from the advancements of bioinformatic pipelines and pharmacogenomic databases. Prioritization and annotation of PGx variants will involve the use of PGx-specific scores, in addition to the ACMG/AMP

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criteria. PGx scores will help to derive drug response predictions that will inform the selection of drug treatment. With proper implementation and user training, NGS will become an essential tool for PGx testing in the clinic (Giannopoulou et al., 2019).

In the era of big data and -omics technologies, the translation of pharmacogenomics in the clinic has yet to be met. Despite the efficiency of current pharmacogenomic tests, the clinical implementation of pharmacogenomic testing remains limited. A few commercial and research pharmacogenomic arrays exist, but these are based on single nucleotide polymorphism (SNP) candidates selected from candidate gene studies and large genome-wide association studies (GWAS). In contrast, next-generation sequencing will soon be part of the clinical reality, and one of the first areas that will be readily applicable is the rationalization of drug use. As many diseases involve multiple genes, clinical laboratories already perform routine testing of several hundred genes simultaneously using NGS. Since pharmacogenes can also affect disease progression and drug response, application of next-generation sequencing in pharmacogenomics will vary from targeted pharmacogene resequencing in low resource settings to a comprehensive pre-emptive pharmacogenomics format in countries where NGS is part of the routine practice for disease genetic diagnosis.

4.2. Microarray Technology

Microarrays containing oligonucleotides representative of the entire human genomic DNA sequence were used to assess the genotypes of all 10 of the major CYP450 genes. The pharmacogenomic microarray was applied to individual patients to assess their CYP450 genotypes prior to prescribing drugs that are substrates of these enzymes. The assessment of multiple CYP450 genotypes with a single microarray can help to avoid adverse drug reactions caused by interindividual variability in CYP450 activities. The microarray technology represents a promising method for pharmacogenomic applications in clinical settings (Li et al., 2008). The system for pharmacogenomic microarrays for assessing genotypes of 10 major CYP450 genes was developed. Microarrays containing 2,884 oligomer probes specifically designed to interrogate about 1,080 single nucleotide polymorphisms (SNPs) in all 10 CYP450 genes were fabricated. A 13-chemical, 114-oligomer set of 25-mer oligonucleotides was used to create a microarray containing probes for amplifying and assessing multiple CYP450 SNPs with a single PCR and hybridization. The feasibility of the microarray-based CYP450 test was demonstrated in a clinical pilot study with 21 cancer patients using a pharmacogenomic approach to individualize chemotherapy.

5. Challenges and Limitations in Pharmacogenomic Testing

Despite the promise of PGx testing to improve patient outcomes, there are many challenges to its implementation in clinical practice. In addition to concerns about the clinical validity, clinical utility, and cost effectiveness of many PGx tests, there are issues around education,

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professionalism, standards, and regulation ((Gouri) Mukerjee et al., 2018). In many cases, clinicians lack knowledge of how to interpret PGx test results or how the tests relate to specific medications. Guidelines for medication therapy based on PGx testing have been developed, but these tests are not universally adopted and many prescribers do not receive training in how to interpret them. Pharmacogenomic results may also need to be interpreted in light of other clinical and environmental factors. In non-genomic medicine, it is common for multiple test results to be aggregated in a report that informs a treatment decision, but aggregation of pharmacogenomic results with other tests is less common. Finally, the rapid pace of PGx research creates challenges for the effective translation and implementation of this knowledge into the clinical setting.

One of the more serious concerns regarding the clinical validity of PGx tests is test integrity. There have been reported instances where companies offering PGx tests provide no statistically valid evidence that the tests are accurate. Misleading advertising can exaggerate the ability of PGx testing to assess the risk of adverse drug reactions or other clinical outcomes. Genetic testing in general is a target for fraud. The value of pharmacogenomic tests in improving clinical care or patient outcomes is still unclear for many tests. Pre-emptive multiplex PGx testing before treatment has the greatest potential to realize the test's benefits, but currently most of the clinical implementation of PGx testing occurs reactively after a poor clinical outcome. Concerns have been raised regarding the cost-effectiveness of some of the PGx tests already on the market – particularly in light of the modest benefits observed.

5.1. Interpretation of Results

Pharmacogenomic test results can be classified into one or more matching categories. A matching category indicates that the test result fits a previously generated categorization (e.g. "normal metabolizer" of CYP2D6). An interpretation that derives from the matching category can be translated into recommendations for a specific intervention, such as dose adjustment or selection of an alternative drug (HN van Schaik, 2014). In general, pharmacogenomic tests have two purposes: to identify those patients with a genetic variation who are at high risk for developing toxicity or treatment failure and to identify those patients without the pharmacogenomic variation who can be treated safely with the standard doses. Currently the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) require risk evaluation and mitigation strategies for drugs with a pharmacogenomic label concerning the interpretation of results. This means that the labeling of these drugs must include information on how the pharmacogenomic test should be interpreted in order to minimize the risk of adverse events or treatment failure. However, these requirements only apply to pharmacogenomic tests conducted on genes affecting drug metabolism and clearance. Currently, no stand-alone pharmacogenomic tests have FDA premarket approval.

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Most pharmacogenomic tests are currently available as laboratory-developed tests, which are not subject to FDA oversight on how pre-analytical, analytical, or interpretation aspects of these tests should be controlled.

5.2. Cost and Accessibility

Every year in BC over 200,000 people are admitted to hospitals due to adverse drug reactions (ADRs), costing an estimated $49 million per year. Many ADRs can be avoided through better management of drug therapy. There are approximately 300,000 physicians and 580 community pharmacies in the US. The American Pharmacists Association acknowledged the importance of integrating genomics with medication therapy management programs to optimize patient drug therapy, as pharmacists have the most training in pharmacogenomics of any healthcare professional and the greatest accessibility to patients (Breaux et al., 2020).

Implementation of point-of-care pharmacogenomic (PGx) testing in community pharmacies has been challenged by several factors including low acceptance of pharmacist recommendations by physicians, mixed patient receptivity, low reimbursement rates to pharmacists for medication therapy management, inadequate human resources to deliver medication therapy management in community pharmacies, and pharmacy layout not conducive to private consultations. Community pharmacies are well-situated to provide PGx testing services at the point-of-care, given patient accessibility and established relationships between pharmacists and patients. However, there are barriers to the uptake of PGx testing including the cost of PGx testing, which generally ranges from $200–$500 for 5–18 genes depending on the provider, often left to consumers to pay as insurers are hesitant to cover genetic testing for non-diagnostic purposes. Other concerns include data security and privacy of genomic data, as well as the clinical impact of genotype-guided therapy on patient outcomes.

The American Society of Clinical Oncology recommends that patients receiving treatment with irinotecan should have their UGT1A1 genotype assessed because this is associated with the drug's toxicities. Access to guideline-recommended PGx tests was explored from the perspective of providers and patients, focusing on challenges in obtaining tests that inform treatment decisions about cancer medications (Chen Wu et al., 2017). Gaps in communication between patients and providers about costs and the limitations of means to manage costs were highlighted.

6. Ethical and Legal Considerations

Personalized medicine offers great promise for improving the safety and efficacy of drug therapy, but several important ethical and public policy concerns need to be considered before this promise can be realized. Considerable progress has been made in understanding how genetic variation influences individual differences in responses to drugs and in creating

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DNA-based tests that predict an individual's response to specific medications (S. Gershon et al., 2014). This knowledge and technology can be incorporated into clinical practice during the entire process of drug development and implementation, from the initial choice of drug to be prescribed, use of the drug, and monitoring for potential adverse drug reactions (ADRs). The inclusion of pharmacogenomic data in drug regulatory submissions to health authorities is now required in many countries.

The incorporation of pharmacogenomic data into drug development and the clinical practice raises a number of important policy and ethical questions involving pharmacogenomic research, public health, clinical practice, drug regulation, and the pharmaceutical industry. These issues are particularly important in regard to public vs corporate ownership and access to the results of large-scale genomic and pharmacogenomic research because of the potential public health benefits. This is similar to the genome sequencing of other infectious disease pathogens, which are publicly deposited in the GenBank database after consideration of the bioweapons research concerns.

6.1. Informed Consent

Patient comprehension of informed consent in pharmacogenomic testing is most impacted by health literacy and understanding of pharmacogenomics. Testing location, type of test, and a patient's race and ethnicity only have a small impact on comprehension. Efforts to enhance patient comprehension should build upon strengths instead of addressing perceived deficits (Pereira et al., 2024). Currently, there is no standard approach to obtaining informed consent for pharmacogenomic tests. The most common approach is to provide a written consent form, which is usually supplemented with a pre-test education session (Mills & B Haga, 2018). While this approach often suffices, issues still arise when obtaining informed consent—most commonly, a lack of understanding of the purpose, type and implications of the pharmacogenomic test being conducted. Informed consent should be conceptualized as an ongoing relationship between a clinician and patient, rather than simply a 'one-off' process. Findings suggest that clinicians should devote efforts to protecting patients from feeling overwhelmed by too much information. Alternative strategies of obtaining informed consent that present information in different ways show promise for improving patient comprehension. However, there is insufficient data to understand how feasible these methods are in practice.

6.2. Data Privacy

As the implementation of pharmacogenomic testing becomes more widespread, it is important to consider the privacy and security of genetic information. Unlike other health data, genetic information is unique to an individual and cannot be changed (Tucker, 2008). This raises concerns about potential discrimination from employers or insurers if genetic data

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is misused. Currently, there are limited laws in place to protect genetic information, but these laws have holes and limitations. With genetic technology advancing rapidly, it is essential for policymakers to address these data privacy issues in relation to pharmacogenomic testing (HN van Schaik, 2014). To ensure the safety and security of this life-altering information, the input of genetic technology experts should be considered when drafting new legislation.

7. Future Directions in Pharmacogenomic Testing

Pharmacogenomics is one of many emerging fields in medicine and healthcare that is either directly or indirectly related to the genomics revolution. Pharmacogenomics has emerged as a subfield of pharmacology and genomics, thus influencing drug discovery, development, and clinical practice. Since 2016, the Food and Drug Administration (FDA) has permitted the marketing of commercially available clinical pharmacogenomic tests in the USA. Pharmacogenomic testing has the potential to critically improve therapy outcomes and reduce adverse drug reactions (ADRs) (Elewa & Awaisu, 2019). The application of pharmacogenomics in clinical settings is often referred to as "pharmacogenomic testing" or "clinical pharmacogenomics" when several genes are tested simultaneously. As the understanding of the genomic basis of drug action and disposition expands, pharmacogenomic testing may be performed routinely in clinical practice.

However, despite a wealth of scientific evidence, pharmacogenomic testing has not been adopted in routine clinical practice for all drugs with pharmacogenomic implications. The progress has been slow partly due to the diversity in translation from bench-to-bedside across pharmacogenomic systems and partly due to system-specific challenges (HN van Schaik, 2014). There are important questions related to the future implementation of pharmacogenomic testing in routine clinical practice. What strategies should be developed to ensure that pharmacogenomic testing systems are successfully implemented in future clinical practice? What pharmacogenomic tests and procedures should be prioritized in implementation? What healthcare professional roles are critical in implementation? What challenges and hurdles should be considered and how can they be overcome?

7.1. Precision Medicine Initiatives

Personalized medicine is an emerging approach that considers patients' individual differences in genes, environments, and lifestyles. Pharmacogenomics is one of the components of personalized medicine, which is defined as the study of the interindividual variability in drug response due to the effect of genetic or genomic information. Pharmacogenomics is one of the emerging approaches to precision medicine, tailoring drug selection and dosing to the patient's genetic features (Cecchin & Stocco, 2020). Several pharmacogenetic guidelines have been published, but the uptake in clinical practice is still poor. Many coordinated international efforts are ongoing to overcome the existing barriers to pharmacogenomic

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implementation. The Clinical Pharmacogenetics Implementation Consortium publishes freely available evidence-based pharmacogenetic guidelines for clinicians. The FDA pharmacogenomic voluntary participation program encourages drug manufacturers to submit pharmacogenomic information to the FDA as part of the new drug application. The EHR4CR and EMR4PG projects are developing models for using electronic health records in pharmacogenomic research. The 100,000 Genomes Project in England and All of Us Research Program in the US sequencing a diverse cohort of patients will provide new tools for pharmacogenomic research. Despite the international efforts, the uptake of pharmacogenetic testing in routine care remains suboptimal in many countries (Celsa Peña-Martín et al., 2022). The main factors that limit implementation are the lack of awareness about testing among healthcare providers, cost-effectiveness concerns, and a lack of access to testing services. There are solutions to alleviate some of these problems. For example, several large ongoing or planned pharmacogenomic implementation studies may demonstrate the clinical utility of pharmacogenetic testing in adults and children with cancer, epilepsy, or psychiatric disorders. Education of healthcare providers is essential to improve awareness and understanding of the potential benefits of pharmacogenomic testing. The establishment of point-of-care testing services and the integration of pharmacogenomic testing into routine genetic services will facilitate access to testing. However, several concerns about pharmacogenomic testing warrant caution, and these concerns should be openly discussed.

7.2. Personalized Drug Development

Pharmacogenomics is the study of how genes affect a person's response to drugs. It holds the promise of using an individual's genomic profile to predict safe and effective doses of drugs in disease prevention and treatment. Drug metabolism and pharmacokinetics have long been recognized as important determinants of efficacy and toxicity in drug development.

Implementation of pharmacogenomics in clinical practice has been constrained by challenges in demonstrating clinical utility and significant evidence gaps in validating pharmacogenomic biomarkers. Nevertheless, there are compelling reasons to incorporate pharmacogenomic strategies in the drug development process. Emerging trends in drug development, such as the shift towards orphan drugs, "first-in-class" drugs, and targeted therapy, and the increasing role of safety in drug discontinuation, synergistically fortify the epidemiological basis and scientific rationale for incorporating pharmacogenomic strategies (W. Francis Lam, 2013).

Pharmacogenomic-guided drug therapy is currently limited to the "one size fits all" approach. Nonetheless, pharmacogenomics has enormous potential to achieve drug therapy that is safe, effective, and economical when translated into clinical practice and routine testing. There are compelling reasons to incorporate pharmacogenomic strategies in the drug development process. Valuing the pharmacogenomic landscape and the developmental impact of candidate drug-genes will avert failed drug development programs, restrict the post-market enforcement

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of precautions, and mitigate the risk of adverse events associated with uncharacterized drug-gene pairs (de Leon, 2009).

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