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UPDATE

Pharmacogenomics : tailoring drug therapy to individual patients

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Pharmacogenomics, Personalized medicine, Drug response, Genetic variations, Clinical applications

Abstract

Pharmacogenomics, the study of how individual genetic variations influence drug response, holds tremendous potential for personalized medicine. This comprehensive literature review explores the current landscape of pharmacogenomics, focusing on its role in tailoring drug therapy to individual patients.

The introduction provides an overview of pharmacogenomics, its definition, and historical development. The subsequent sections delve into key subtopics, including the influence of pharmacogenomic variants on drug metabolism, the identification of genetic biomarkers for drug efficacy and safety, pharmacogenomic testing approaches, and clinical applications in various healthcare settings.

Ethical, legal, and social implications (ELSI) surrounding pharmacogenomics are discussed, along with future directions and challenges in this field. Through a meticulous analysis of existing research articles, clinical guidelines, and reviews, this literature review highlights the significance of pharmacogenomics in optimizing drug therapy, improving patient outcomes, and fostering the era of precision medicine.

Introduction and the text

Pharmacogenomics is an emerging field of study that investigates the influence of individual genetic variations on drug response. It encompasses the interdisciplinary approach of pharmacology and genomics to optimize drug therapy for individual patients [1]. Understanding the genetic basis of drug response is of paramount importance as it enables the tailoring of treatments to maximize efficacy and minimize adverse reactions [2].

The scope of pharmacogenomics extends beyond the identification of single gene-drug interactions. It involves the study of genetic variations that influence drug metabolism, drug target interactions, and drug transport mechanisms [3]. By uncovering the genetic factors responsible for interindividual variability in drug response, pharmacogenomics facilitates the development of personalized medicine approaches [4]. The significance of individual genetic variations in drug response cannot be overstated. Genetic polymorphisms in drug-metabolizing enzymes, such as the cytochrome P450 (CYP) superfamily, can lead to altered drug metabolism rates and subsequent variations in drug efficacy and toxicity [5]. Additionally, genetic variations in drug targets and transporters can affect drug binding affinity and distribution, thereby influencing therapeutic outcomes [6].

The historical background of pharmacogenomics traces back several decades. The field gained momentum in the mid-20th century with the discovery of inherited traits affecting drug metabolism, exemplified by the classic work on the inherited deficiency of glucose-6-phosphate dehydrogenase and its impact on primaquine-induced hemolysis [7]. The advent of molecular genetics and the Human Genome Project further accelerated progress in pharmacogenomics, enabling the identification of genetic variants associated with drug response [8]. In recent years, advancements in high-throughput genotyping technologies and cost-effective sequencing methods have enhanced our ability to identify genetic variations relevant to drug response. These technological breakthroughs, coupled with the increasing availability of large-scale genomic databases, have paved the way for the translation of pharmacogenomics into clinical practice [9].

II. Pharmacogenomic variants and drug metabolism

Drug metabolism, a critical process in determining drug response, is influenced by genetic variants in key drug-metabolizing enzymes, particularly the cytochrome P450 (CYP) superfamily. Cytochrome P450 enzymes play a vital role in the biotransformation of a wide range of medications, including many commonly prescribed drugs [5]. Genetic polymorphisms in CYP enzymes can lead to variations in drug metabolism rates, resulting in interindividual differences in drug efficacy, toxicity, and overall response [10]. Among the CYP enzymes, CYP2D6, CYP2C9, and CYP2C19 have garnered substantial attention due to their involvement in the metabolism of numerous clinically significant drugs. For instance, CYP2D6 is responsible for the metabolism of several antidepressants (e.g., selective serotonin reuptake inhibitors), antipsychotics (e.g., risperidone), and antiarrhythmic agents (e.g., flecainide) [11].

Genetic variations in CYP2D6 can lead to altered enzyme activity, resulting in the classification of individuals into different phenotypic groups, such as poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), or ultrarapid metabolizers (UMs) [12]. These phenotypic variations can impact drug concentrations, therapeutic outcomes, and the risk of adverse drug reactions(as illustrated in Table 1).

Table 1. the table provides a summary of genetic polymorphisms known to significantly impact drug response, outlining the associated drugs and the resulting clinical consequences

Genetic polymorphism	Drug (s) involved	Clinical consequences
CYP2D6 *4/*4	Codeine, Tamoxifen	Reduced drug metabolism, decreased efficacy
CYP2C19 *2/*2	Clopidogrel, Proton Pump, inhibitors	Impaired drug activation, reduced efficacy
VKORC1 -1639G>A	Warfarin	Altered sensitivity, risk of bleeding
HLA-B*5701	Abacavir (HIV drug)	Hypersensitivity reaction, severe adverse events
TPMT *2/*3A	Thiopurines (e.g., Azathioprine)	Increased risk of myelosuppression
UGT1A1 *28	Irinotecan	Increased risk of toxicity, neutropenia
HLA-B*1502	Carbamazepine	Risk of severe skin reactions, e.g., SJS/TEN
SLCO1B1 *5/*5	Statins (e.g., Simvastatin)	Increased risk of myopathy
NAT2 Slow Acetylator	Isoniazid, Hydralazine	Altered drug metabo lism, risk of toxicity
MTHFR C677T	Methotrexate	Altered folate metabo lism, efficacy concerns

Similarly, genetic variants in CYP2C9 are known to affect the metabolism of drugs such as warfarin, a widely prescribed anticoagulant. Variants in CYP2C9, particularly CYP2C9*2 and CYP2C9*3, are associated with reduced enzyme activity, resulting in decreased drug clearance and an increased risk of bleeding events in patients receiving warfarin therapy [13].

CYP2C19 is another crucial enzyme involved in the metabolism of numerous drugs, including proton pump inhibitors (e.g., omeprazole), selective serotonin reuptake inhibitors (e.g., escitalopram), and antiplatelet agents (e.g., clopidogrel). Genetic variations in CYP2C19 can lead to altered enzyme activity, resulting in distinct metabolizer phenotypes, with poor metabolizers being associated with reduced drug metabolism and potential treatment failure [14].

Apart from the CYP superfamily, other genetic variants can also impact drug metabolism pathways. For instance, the thiopurine methyltransferase (TPMT) gene plays a crucial role in the metabolism of thiopurine drugs like azathioprine and mercaptopurine, commonly used in the treatment of autoimmune diseases and malignancies. Variants in the TPMT gene, such as TPMT*2 and TPMT*3A, result in reduced enzyme activity, leading to higher drug concentrations and an increased risk of myelosuppression [15]. Genetic testing for TPMT variants before initiating thiopurine therapy allows for personalized dosing to optimize efficacy while minimizing toxicity.

Additionally, the uridine diphosphate glucuronosyltransferase (UGT) enzymes, particularly UGT1A1, are involved in the glucuronidation and subsequent elimination of drugs such as irinotecan, a widely used chemotherapeutic agent. A genetic variant in UGT1A1, known as UGT1A1*28, is associated with reduced enzyme activity, resulting in impaired drug clearance and an increased risk of severe myelosuppression and diarrhea in patients receiving irinotecan [16]. Prospective UGT1A1 genotyping can aid in dose adjustments and personalized treatment strategies to mitigate the risk of severe adverse reactions.

Moreover, the multidrug resistance protein 1 (MDR1) gene, also known as ATP-binding cassette sub-family B member 1 (ABCB1), encodes a drug efflux pump that plays a critical role in drug transport and elimination. Genetic variants in MDR1/ABCB1, such as C3435T and G2677T/A, have been associated with altered drug bioavailability and response to various medications, including anticancer drugs, immunosuppressants, and cardiovascular medications [17]. Understanding the impact of MDR1/ABCB1 genetic variants can assist in optimizing drug selection, dosing, and overall treatment outcomes.

III.Genetic biomarkers for drug efficacy and safety

The identification of genetic biomarkers has revolutionized the field of pharmacogenomics by enabling the prediction of drug response and individualizing treatment strategies. Genetic variants in specific genes have been associated with variations in drug efficacy and safety profiles, offering valuable insights into personalized medicine approaches [4].

The identification of genetic biomarkers for predicting drug response is a crucial step toward optimizing therapy. By examining specific gene variants, researchers have uncovered associations between genetic variations and drug response in various therapeutic areas. For instance, genetic variants in the human epidermal growth factor receptor 2 (HER2) gene have been found to predict the response to trastuzumab in breast cancer patients. The amplification or overexpression of HER2 is indicative of a favorable response to trastuzumab, enabling the selection of patients who are most likely to benefit from this targeted therapy [18].

Similarly, the presence of specific mutations in the BCR-ABL1 gene is used to identify chronic myeloid leukemia (CML) patients who are likely to respond to tyrosine kinase inhibitors such as imatinib [19].

Moreover, genetic markers associated with adverse drug reactions have shed light on the interplay between genetic variations and drug safety. For instance, the human leukocyte antigen (HLA) gene region has been implicated in severe cutaneous adverse drug reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, which can occur in response to medications such as carbamazepine and allopurinol. Certain HLA-B alleles, such as HLA-B*15:02 and HLA-B*57:01, have been identified as risk factors for these reactions, allowing for pre-treatment screening and the implementation of preventive measures [20].

Furthermore, pharmacogenomic studies have uncovered associations between specific gene variants and drug efficacy in diverse therapeutic areas. For example, variants in the VKORC1 and CYP2C9 genes have been linked to warfarin response and dosage requirements. Genetic testing for VKORC1 and CYP2C9 variants allows for individualized warfarin dosing to achieve optimal anticoagulation while minimizing the risk of bleeding or thromboembolic events [21].

Advancements in genomics have facilitated the discovery of genetic biomarkers associated with drug efficacy and safety across various therapeutic areas. For instance, in the field of oncology, the identification of genetic mutations in the epidermal growth factor receptor (EGFR) gene has revolutionized the treatment of non-small cell lung cancer (NSCLC). Specific EGFR mutations, such as exon 19 deletions and the L858R substitution, have been linked to increased sensitivity to EGFR tyrosine kinase inhibitors (TKIs) like erlotinib and gefitinib. Consequently, EGFR mutation testing has become an essential diagnostic tool for guiding treatment decisions in NSCLC, enabling the selection of patients who are more likely to respond favorably to targeted therapies [22].

Similarly, genetic biomarkers have been identified for predicting response to immunosuppressive medications used in transplantation. The gene encoding thiopurine S-methyltransferase (TPMT) plays a crucial role in the metabolism of thiopurine drugs such as azathioprine and mercaptopurine. Genetic variants in TPMT, such as TPMT*2 and TPMT*3A, are associated with reduced enzyme activity, leading to increased drug toxicity and a higher risk of myelosuppression. TPMT genotyping is now recommended prior to initiating thiopurine therapy to guide dosage adjustments and prevent severe adverse reactions [15].

Furthermore, the concept of pharmacogenomics has also extended to cardiovascular medicine. Genetic variations in the gene encoding the enzyme CYP2C19 have been associated with variable response to antiplatelet therapy with clopidogrel, commonly prescribed after percutaneous coronary intervention (PCI). Patients with loss-of-function alleles, such as CYP2C19*2, exhibit reduced activation of clopidogrel and may have an increased risk of adverse cardiovascular events. Genotyping for CYP2C19 variants allows for tailored antiplatelet therapy, with alternative agents like ticagrelor or prasugrel being recommended for patients with identified loss-of-function variants [23].

These examples underscore the clinical significance of genetic biomarkers in predicting drug response and guiding treatment decisions. The integration of pharmacogenomic information into routine clinical practice empowers healthcare providers to make personalized therapeutic choices based on an individual's genetic profile. By selecting the most effective and safe medications for each patient, pharmacogenomics has the potential to enhance treatment outcomes, minimize adverse events, and optimize the use of healthcare resources [2].

IV. Pharmacogenomic testing approaches

Pharmacogenomic testing plays a vital role in translating genetic information into actionable clinical insights, enabling personalized medicine approaches. Various techniques and methodologies are employed for pharmacogenomic testing, each with its own strengths and limitations [24]. Genotyping, which involves the analysis of specific genetic variants, is commonly used for pharmacogenomic testing. Techniques such as polymerase chain reaction (PCR), DNA microarrays, and next-generation sequencing (NGS) facilitate the detection of genetic variations associated with drug response [25]. PCR-based methods, including allele-specific PCR and real-time PCR, offer high specificity and sensitivity for targeted genotyping. DNA microarrays enable simultaneous testing for multiple genetic variants, while NGS allows for comprehensive analysis of the entire genome or specific gene regions [26].

Challenges and limitations exist in implementing pharmacogenomic testing in routine clinical practice. One significant challenge is the interpretation and clinical relevance of genetic variants. While many variants have been associated with drug response, not all have been definitively linked to clinical outcomes or have established therapeutic guidelines. Additionally, the presence of multiple genetic variants and the potential interactions among them further complicate interpretation [27]. Standardization of pharmacogenomic testing platforms, variant classification, and reporting guidelines are crucial for ensuring consistent and accurate results across different laboratories and clinical settings.

Another limitation is the cost-effectiveness of pharmacogenomic testing. The expenses associated with genetic testing, particularly with NGS-based approaches, can be a barrier to widespread implementation. However, as the costs of sequencing technologies continue to decline, and with the development of targeted genotyping panels, the economic feasibility of pharmacogenomic testing is improving [28].

Integration of pharmacogenomic testing into clinical practice poses another challenge. Healthcare professionals require education and training to understand the implications of pharmacogenomic test results, interpret them in the context of individual patient characteristics, and apply the information to guide treatment decisions [29]. Furthermore, the development of clinical decision support systems and electronic health record (EHR) integration is crucial for seamless integration of pharmacogenomic information into the clinical workflow. Realizing the full potential of pharmacogenomic testing requires collaboration among researchers, clinicians, laboratory professionals, and policymakers to address these challenges and facilitate widespread adoption.

Despite these challenges, efforts are underway to integrate pharmacogenomic testing into routine clinical care. Several institutions and healthcare systems have implemented pharmacogenomic testing programs, and guidelines and recommendations for specific drug-gene pairs have been developed by organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) [15]. Collaborative research initiatives are exploring the clinical utility and cost-effectiveness of pharmacogenomic testing, providing valuable evidence to guide its integration into routine care.

V. Clinical applications of pharmacogenomics

Pharmacogenomic testing has demonstrated its clinical utility in guiding drug therapy decisions, optimizing treatment outcomes, and improving patient safety. Several drugs have been identified for which pharmacogenomic testing is recommended to aid in personalized prescribing [30]. For instance, the anticoagulant drug warfarin has been extensively studied in the context of pharmacogenomics. Genetic testing for variants in the VKORC1 and CYP2C9 genes is recommended to predict individualized warfarin dosing requirements and minimize the risk of bleeding or thrombotic events [15]. Similarly, the antiplatelet agent clopidogrel requires pharmacogenomic testing for the CYP2C19 genotype to identify patients who may exhibit reduced drug response and guide the selection of alternative therapies like ticagrelor or prasugrel [23].

Case studies have illustrated the impact of pharmacogenomics on patient outcomes. One notable example is the use of pharmacogenomic testing in HIV/AIDS treatment. The Human Immunodeficiency Virus (HIV) can develop resistance to antiretroviral medications over time. However, genotypic testing for drug resistance-associated mutations can guide the selection of optimal antiretroviral regimens, improving treatment response and reducing virologic failure rates [31]. Additionally, in the field of psychiatry, pharmacogenomic testing for antidepressant and antipsychotic medications has shown promising results. Tailoring drug therapy based on individual genetic profiles has been associated with improved treatment response rates and reduced side effects, leading to enhanced patient outcomes in psychiatric disorders [32].

The implementation of pharmacogenomics varies across different healthcare settings. In specialized areas such as oncology, pharmacogenomic testing has become an integral part of treatment decisions. Tumor genomic profiling enables the identification of specific genetic alterations that drive tumor growth, guiding the selection of targeted therapies or clinical trial participation [33]. In primary care settings, pharmacogenomic testing is increasingly being adopted for drugs commonly prescribed, such as antidepressants and analgesics, to optimize treatment outcomes and improve patient safety [34]. Furthermore, pharmacogenomic testing has gained traction in the field of transplantation, where it assists in tailoring immunosuppressive therapy based on individual genetic profiles, thereby enhancing graft survival rates [35].

Efforts to integrate pharmacogenomics into routine clinical care have been supported by the development of guidelines and clinical decision support tools. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have provided evidence-based recommendations for specific drug-gene pairs, facilitating the interpretation of pharmacogenomic test results and guiding treatment decisions [36]. The integration of pharmacogenomics into electronic health records (EHRs) and clinical decision support systems is enabling healthcare providers to access and apply pharmacogenomic information seamlessly in their daily practice, enhancing the implementation of personalized medicine approaches.

The clinical applications of pharmacogenomics extend beyond specific drug-gene pairs. For instance, in the field of anesthesia, pharmacogenomic testing has shown promise in predicting individual responses to various anesthetic agents and analgesics. Genetic variants in genes encoding drug-metabolizing enzymes and drug targets can influence drug efficacy, side effects, and recovery time. Tailoring anesthetic and analgesic regimens based on individual genetic profiles may optimize pain management and minimize adverse events, leading to improved patient satisfaction and outcomes [37]. Furthermore, pharmacogenomic testing has demonstrated utility in psychiatric disorders such as major depressive disorder and schizophrenia. Antidepressants and antipsychotics exhibit variable response rates and side effect profiles among individuals. Pharmacogenomic testing can help identify genetic variations associated with drug metabolism and drug targets, assisting in the selection of appropriate medications and dosages for optimal therapeutic outcomes. This personalized approach to psychiatric medication management has the potential to improve treatment response rates and minimize the burden of side effects [38].

The implementation of pharmacogenomics in different healthcare settings has witnessed varying degrees of success. In specialized clinics and academic medical centers, where resources and expertise are readily available, pharmacogenomic testing programs have been effectively integrated into patient care workflows. Clinical decision support systems embedded within electronic health records assist healthcare providers in interpreting genetic test results and making informed treatment decisions based on available evidence and guidelines [39].

However, challenges persist in more resource-limited settings, where limited access to genetic testing infrastructure and lack of specialized expertise pose barriers to widespread implementation. Collaborative efforts among healthcare systems, regulatory bodies, and policymakers are essential to address these challenges and facilitate equitable access to pharmacogenomic testing.

Case studies and real-world evidence have highlighted the impact of pharmacogenomics on patient outcomes. For instance, a study examining the implementation of preemptive pharmacogenomic testing in a large healthcare system demonstrated significant reductions in adverse drug reactions and hospitalizations, leading to cost savings and improved patient care [9].

These examples underscore the potential of pharmacogenomic testing to enhance treatment outcomes, reduce healthcare costs, and improve patient safety across diverse clinical scenarios. As the field of pharmacogenomics continues to evolve, ongoing research and collaboration are necessary to expand the repertoire of drugs with pharmacogenomic implications and to refine guidelines for clinical implementation. Pharmacogenomic testing has the potential to transform healthcare by enabling personalized and precise medication selection and dosing, thus optimizing therapeutic outcomes and reducing the risk of adverse drug reactions.

VI. Ethical, legal, and social implications of pharmacogenomics

As pharmacogenomic testing becomes more prevalent, it raises important ethical, legal, and social considerations that must be addressed to ensure responsible and equitable implementation. One of the key concerns is the protection of patient privacy and the secure handling of genetic information. Given the sensitive nature of genetic data, robust privacy safeguards must be in place to prevent unauthorized access and misuse. Ethical frameworks emphasize the importance of informed consent, ensuring that patients understand the implications of genetic testing, the potential risks, and the limitations of test results. Healthcare providers and researchers must prioritize the secure storage and responsible use of genetic information, adhering to stringent data protection regulations and ethical guidelines [40]. The issue of health disparities and access to pharmacogenomic testing also requires attention. Genetic testing technologies and resources may not be equally available across diverse populations, leading to disparities in healthcare delivery and outcomes. Ensuring equitable access to pharmacogenomic testing is crucial to prevent exacerbating existing healthcare disparities. Efforts should focus on addressing barriers such as cost, infrastructure, education, and cultural sensitivity. Collaborations between stakeholders, including policymakers, researchers, healthcare providers, and patient advocacy groups, are necessary to develop strategies that promote inclusivity and mitigate disparities in the implementation of pharmacogenomics [30].

Policy and regulatory frameworks play a vital role in governing the ethical and responsible use of pharmacogenomic testing. National and international bodies have developed guidelines and regulations to guide the practice of pharmacogenomics. These frameworks address issues such as laboratory quality standards, reporting of test results, interpretation of genetic variants, and the integration of pharmacogenomic information into clinical practice. They aim to ensure the accuracy and reliability of test results, protect patient rights, and promote evidence-based decision-making. Policymakers should continuously evaluate and update these frameworks to keep pace with the evolving field of pharmacogenomics and address emerging ethical, legal, and social challenges [41].

Additionally, public engagement and education are crucial in fostering understanding and acceptance of pharmacogenomic testing. Public perceptions, beliefs, and attitudes toward genetic testing can influence its adoption and implementation.

Open dialogue between researchers, healthcare providers, policymakers, and the public can help address concerns, dispel misconceptions, and promote awareness about the benefits and limitations of pharmacogenomics. Furthermore, initiatives that promote health literacy and provide accessible educational resources can empower individuals to make informed decisions about genetic testing and participate actively in their healthcare [42].

Addressing the ethical, legal, and social implications of pharmacogenomics is paramount to ensure its responsible and equitable integration into clinical practice. By considering issues related to privacy, consent, access, and policy, healthcare systems can navigate the complexities of pharmacogenomics while safeguarding patient rights and promoting equal opportunities for improved treatment outcomes.

VII. Future directions and concluding remarks

Pharmacogenomics is a rapidly evolving field, and several future directions and challenges lie ahead as researchers and healthcare providers seek to maximize its potential. Advances in technologies and their application to pharmacogenomics are poised to shape the future of personalized medicine. The emergence of novel sequencing technologies, such as single-molecule sequencing and long-read sequencing, holds promise for more comprehensive and accurate genetic variant detection, enabling deeper insights into the relationships between genetic variations and drug response [43]. Moreover, the integration of multi-omics data, including genomics, transcriptomics, and metabolomics, can provide a more comprehensive understanding of individual variations in drug metabolism and response, offering a holistic approach to personalized therapeutics [44].

The seamless integration of pharmacogenomic information into electronic health records (EHRs) is crucial for realizing the full potential of personalized medicine. The inclusion of pharmacogenomic test results in EHRs allows healthcare providers to access and utilize genetic information at the point of care, facilitating informed treatment decisions and minimizing potential medication-related adverse events. Integration of pharmacogenomic data into EHRs can also enable clinical decision support systems to provide real-time alerts and tailored recommendations based on an individual's genetic profile, further enhancing precision medicine approaches [39].

Despite significant progress, there are several areas that require further research and development. One key area is the expansion of evidence-based guidelines for pharmacogenomic testing and interpretation. While guidelines for specific drug-gene pairs exist, there is a need for broader guidelines that encompass a wider range of drugs and genetic variations. Additionally, the translation of pharmacogenomic discoveries into clinical practice requires robust evidence on the clinical utility and cost-effectiveness of testing. Prospective studies evaluating the impact of pharmacogenomic-guided therapy on patient outcomes, healthcare utilization, and cost-benefit analysis are crucial to build a strong evidence base for widespread implementation [45].

Furthermore, addressing the challenges associated with data management and analysis is paramount. The integration and analysis of large-scale pharmacogenomic datasets, coupled with electronic health records, necessitate the development of robust bioinformatics tools and scalable infrastructure. Collaboration among researchers, bioinformaticians, and data scientists is essential to optimize data storage, processing, and interpretation, enabling efficient utilization of pharmacogenomic data for clinical decision-making [46].

Another important direction for future research is the exploration of additional genetic factors beyond single-nucleotide polymorphisms (SNPs). Copy number variations, epigenetic modifications, and gene-gene interactions are increasingly recognized as key contributors to interindividual variability in drug response. Understanding the complex interplay of these factors and their impact on pharmacogenomics will provide a more comprehensive understanding of individualized drug therapy and treatment outcomes [47].

In summary, the future of pharmacogenomics holds great promise in revolutionizing personalized medicine. Advances in technologies, integration into electronic health records, the development of evidence-based guidelines, and further research into genetic variations and interactions are crucial for the successful implementation of pharmacogenomics, enabling healthcare providers to deliver precise and individualized therapeutic interventions, ultimately improving patient outcomes.

Conflicts of interest

The author declare no conflicts of interest to declare.

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