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Pharmacogenomics in Personalized Oncology: From Biomarker Discovery to Clinical Implementation

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ABSTRACT

Pharmacogenomics has emerged as a cornerstone of personalized oncology, enabling the optimization of drug selection and dosing based on individual genetic profiles. This review traces the journey from biomarker discovery to clinical implementation, covering technologies such as next-generation sequencing (NGS), liquid biopsy, and single-cell RNA sequencing. Challenges related to data interpretation, integration into clinical practice, and ethical considerations in genomic data handling are critically discussed. Case studies highlighting success stories in targeted therapies, such as EGFR inhibitors and PARP inhibitors, are included.

Keywords: Biomarkers, Liquid Biopsy, Next-Generation Sequencing, Personalized Oncology, Pharmacogenomics, Precision Medicine, Targeted Therapy

1 Introduction to Pharmacogenomics

PHARMACOGENOMICS (PGx) refers to the study of how an individual's genes affect their response to drugs. PGx is a key component of personalized medicine, where an individual's response to a therapy is predicted by genetic information. Drug response is influenced by both genomic and environmental factors. The genomic component is studied by human genomics, while the environmental component is defined as exposure to any environmental agent not coded within the DNA. Pharmacogenomics can thus be divided into two major branches: germline (heritable variants) and somatic (non-heritable variants) [1].

Germline PGx is the study of genetic variants in metabolizing drug transporters (DMTs) genes and drug target genes associated with the clinical variability of drug therapy. The majority of germline PGx studies have focused on the variability in the metabolizing DMTs, specifically in the cytochrome P450 gene family, although

the study of transporters and target genes has also exploded in the last decade. Somatic PGx differs from germline PGx in that it involves non-heritable variants in DMTs that have a clinical effect in predetermined (pre-treated tumor) tissue only. Most of the study of somatic PGx focused on the presence of mutations in drug target genes and their association with clinical outcomes, while the study of somatic variants in drug metabolizing genes is less extensive [2].

Drug response is estimated by jointly considering the genetic and environmental components, all the while remaining agnostic to environmental agents. A model is used to illustrate how drug response is determined by both the genomic and environmental components, thereby establishing the limits of PGx studies in predicting drug responses in practice. The effectiveness of translating PGx discoveries into practice is contingent upon collaborative efforts between clinical investigators and bench scientists, taking discoveries from clinical studies into the laboratory. These translational efforts will be aided by harnessing the vast amounts of genomic information generated by whole genome sequencing and microarrays, as well as chemical information captured by metabolomics, as shown in Figure 1.

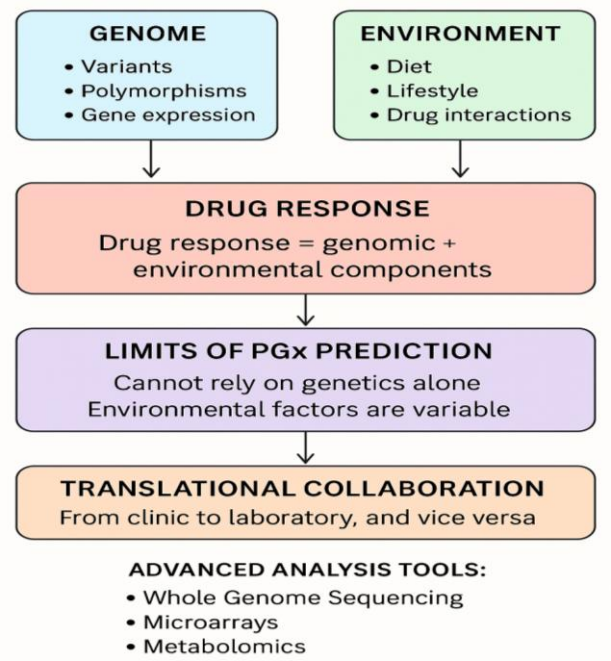

Fig. 1. Pharmacogenomics in practice: from genes to environment to therapy.

2 The Role of Biomarkers in Oncology

Biomarkers are essential in helping to dissect the heterogeneity of cancers and guiding clinical decision making in oncology. Actually, cancer is a heterogeneous disease regarding patient prognosis and response to treatment which has implications for clinical decision making. Currently, several different treatment strategies are used including surgery, radiotherapy, therapy with traditional chemotherapeutics or target drugs and immunotherapy. However, the success of these treatment strategies differs substantially among patients, which is especially true for newly diagnosed disease entities, metastatic disease and screening strategies for preventive treatment. For instance, the 5-th year survival rates after surgical resection of the entire tumor vary substantially within one tumor entity, such as colorectal cancer, in different patient groups. Recently, the incorporation of prognostic biomarkers has substantially improved the classification of the colon cancer patient cohort into different risk groups regarding the outcome after metastasectomy [3]. On a molecular level, the heterogeneity is displayed on multiple levels: genomics, epigenomics, transcriptomics and proteomics features. Especially transcriptomic or genetic tumor characteristics are precision oncology markers which are being successively clinically implemented in oncology like e.g. in colorectal, breast and non-small cell lung cancer. In spite of these substantial advances recent data from clinical trials and community practices suggest that currently established prognostic biomarkers cannot be successfully applied to a substantial percentage of treatment decision making in oncology practice. Therefore, there is a need for novel biomarkers which should address current limitations and provide additional value for patient stratification and treatment decision making in oncology. Ideally, targeted or immunotherapies should be selected based on an individual comprehensive biomarker profile. Promising avenues to target precision oncology with a high medical need include treatment of patients receiving first line therapy and preventatively in low-risk screening settings, where early-stage disease treatment is initiated, and in asymptomatic patients. Unfortunately, the currently approved types of biomarkers cannot be successfully applied to these treatments and patient cohorts [4]. Therefore, there is a need for innovative biomarker candidates in order to achieve precision medicine for all cancer patients. Such candidate signatures should provide a comprehensive quantification of tumor properties addressing treatment efficacy as well as response as a critical selection point, and functionality as conventional imaging techniques do not provide such data.

3 Pharmacogenomics Testing: Methods and Technologies

In the past 25 years, genomic and transcriptomic data from model organisms have laid the groundwork for trans-omics. However, metabolomics a complex and dynamic layer downstream of genomics has been relatively neglected. This neglect is surprising, as metabolomic data reflect time- and environment-dependent changes, unlike more conserved genomic structures. Yet, general mathematical models for analyzing metabolomic data remain limited, restricting deeper understanding of

phenotype variation and metabolic network development. Deep metabolomic profiling of genetically resolved sap-sucking herbivores and their host plants, both independently and together, led to insights into evolutionary pressures and the molecular signatures retained from a long history of co-evolution [5]. In obtaining these insights, the underlying mathematical framework was revealed as anchored on data geometry: while there is a genomic and epigenomic encoding of biological state, a different level of complexity entails by the precision with which prototyping molecules (univocally) connect to lower-order molecular transformations whose abstract inline behaviors are shared across all genomes [4].

Metabolomic data is vector data characterizing non-linear phase-space oddities in which there are preferred coordinates, and for which a temporal sub-virtual space is particularly relevant. Metabolomic data analysis therefore requires addressing curvature in its high manifold dimensions and equivocality. However, the functional representation of classic operations in metabolomics either ignores data geometry through exploratory analysis through linear projections or deemed only necessary along with effective dimensionality expansion as part of deep learning.

4 Key Genetic Variants in Cancer Treatment

In cancer treatment, genetic variants help predict individual responses, including drug efficacy and toxicity. Pharmacogenetics studies how genetic differences influence drug behavior, aiming to improve effectiveness and safety.

Primary oncogenic variants, typically inherited, assess cancer risk and are tested mostly in younger individuals using established guidelines and polygenic risk scores. In contrast, secondary oncogenic variants arise from somatic changes during cancer progression and are useful for evaluating treatment response.

These acquired mutations can lead to structural DNA changes, including rearrangements and copy number alterations, which may create new genes or disrupt existing ones. Amplicons mutagenic DNA fragments can activate pathways that promote cell survival, resist apoptosis, and enhance tumor progression through angiogenesis, invasiveness, and genomic instability.

Identified germline and somatic variations are more important than drug treatment for prediction of treatment response in colorectal cancer patients. Drug treatment in this research is classified into several groups, among which transformation of fifth generation hydrogen containing delocalized 3-hydroxypyridin-4-one derivatives may get some attention. Lack of detection of oncogenic variants, even for those under certain treatment, is an issue for colorectal cancer. Efficacy and toxicity are both essential criteria for evaluating drug response. Genetic reasons for the adverse effect of drug treatment could also be investigated. On the basis of the current literature, developed liver impairment for ovarian cancer may be caused by drug metabolizing variants under treatment of common drug [6]. In the past few decades, it has been established that a polymorphism in the drug target enzyme is the main criteria for therapeutic plan for breast cancer patients. To enhance the clinical utilization of these genetic variants, more regulations, guidelines and recommendations would be much required.

5 Case Studies in Pharmacogenomics

In the past decade, personalized medicine has rapidly advanced, especially in cancer care. Discoveries in genomic alterations have driven the development of diagnostic tests and predictive biomarkers, enabling more precise, less toxic, and more effective targeted therapies for solid tumors. What was once a distant goal has now become central to cancer treatment, with personalized approaches allowing better monitoring and tailored interventions. These advances build on decades of progress in understanding the genetic basis of cancer.

Single nucleotide polymorphisms (SNPs) are the most common type of genetic polymorphisms detected in the human genome. They are predominantly located in non-coding regions and exhibit a high allele frequency (50%) across populations. Attention is being turned to variants located in both exonic and non-coding regions because of their influence over the expression and/or eventual functionality of the gene [4]. Similar to SNPs, aberrant DNA methylation is gaining interest as it represents another epigenetic change increasingly recognized for its importance in cancers and perhaps for pharmacogenomics as well. There are potential challenges related to the integration and interpretation of dynamic pharmacogenomic data. For example, at what frequency and scope should patient samples be analyzed to ensure adequate characterization and robustness of testing. Should variants and aberrations still be regarded as known or novel if they have not been previously described? What is considered appropriate and meaningful knowledge in describing the effect of a variant on drug metabolism, efficacy, or toxicity. The simple transfer of genomic data can present challenges in interpretation and provenance and the measures of risk often differ between the pharmaceutical and the research setting. Despite misconceptions in patients' understanding of their genomic information, pharmacogenomic testing in cancer patients alerted for its relevance would be beneficial in cancer therapy [7].

5.1 Breast Cancer

Breast cancer remains a major cause of morbidity and mortality. It is a heterogeneous disease characterized by distinct natural history, etiology, and response to therapy.

Advances in genomics and molecular biology have greatly improved the understanding of breast cancer tumorigenesis. New technologies and effective and safer chemotherapeutic agents are being developed to achieve target and personalized therapies. While some well-defined biomarkers have been successfully incorporated into the clinical setting, most pharmacogenomic data remain in the preclinical phases of development. It will be important to ensure that continued sequencing activities will be guided by appropriate study design and methodology for the development of validated biomarkers. Incorporation of pharmacogenomic data to the clinical setting has been hindered by a number of limitations. Primarily, results of pharmacogenomic studies have showed variable results. Thus, reaching consensus on associated outcomes with pharmacogenetic markers has been difficult. This may be due to cohort variations secondary to different ethnic groups or improper tumor classification. Future approaches using genome-wide associations may help identify other candidate genes as predictive biomarkers. However, to replicate results, standard patient classification should be based on well-defined breast cancer classification criteria while adopting standard clinical guidelines. This would enable unmasking of confounding factors and hopefully facilitate the transition of using pharmacogenetic markers for targeted therapy in breast cancer. An integrative approach incorporating preventive and predictive biomarkers, risk factors and clinical data, would be the way forward to assisting targeting therapy providing a personalized medicine treatment [8].

Pharmacogenomics in breast cancer evaluates the effect of inherited genomic variation on patient response or resistance to treatment. Genetic variability is commonly measured at the DNA level. These germline variations are polymorphisms that differ by one base pair in the DNA sequence (SNPs). Rare errors in DNA sequence can yield somatic mutations that may alter protein coding sequences, generate novel fusion proteins, or modify non-coding regulatory elements of the genome. Somatic genomic changes in breast tumors can influence rates of apoptosis, cell proliferation, and DNA damage repair, which may have direct effects on response to treatment and survival. To be most effective, personalized medicine must incorporate information from genetic variation and somatic mutations in diseased tissue [9]. Estrogens play an important role in breast cancer by stimulating growth and proliferation of ductal epithelial cells in the breast. The isoforms of the estrogen receptor, ERa and ERb, mediate the responses to estrogens. The status of the estrogen receptor (ER) in breast carcinomas provided one of the earliest avenues for personalized medicine. Hormone-receptor-positive tumors usually respond to agents such as Tamoxifen that block the function of estrogen. Tamoxifen is a potent antagonist of the ER with inhibitory effects on tumor growth. Tamoxifen has been shown to reduce the risk of cancer recurrence by ~50%. For most patients, the benefit of using tamoxifen outweighs the risk of serious side effects; however, a small subgroup of hormone-receptor-positive patients who carry specific variants in the cytochrome P450 2D6 gene (CYP2D6) do not benefit from tamoxifen. The CYP2D6 gene is a key enzyme in the metabolism of tamoxifen to its active metabolite endoxifen. Several DNA variants in CYP2D6 result in poor metabolism of tamoxifen. Patients who carry reduced-function or nonfunctional CYP2D6 alleles have been found to derive inferior therapeutic benefit from tamoxifen. Studies are underway to determine the utility of CYP2D6 genotyping for making clinical decisions about tamoxifen. Alternate forms of directed anti-estrogen therapies for patients with hormone-receptor-positive breast cancer include aromatase inhibitors and compounds such as fulvestrant.

5.2 Lung Cancer

Lung cancer is the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 80% of cases. Genetic mutations in the epidermal growth factor receptor (EGFR) have been recognized as crucial biomarkers in lung cancer diagnostics and therapeutics. Extensive research in NSCLC has highlighted those mutations in the adenomatous polyposis coli gene, B-Raf proto-oncogene serine/threonine kinase, MET, and Kirsten rat sarcoma viral oncogene homolog can serve as predictive biomarkers indicative of sensitivity to therapy. Clinical implications of the therapeutic use of biomarkers are well-established, and since 2014, four targeted therapies have been approved by the U.S. Food and Drug Administration. They include genotyping tests (biomarkers) that detect sensitive mutations in exons 18–21 of ORF2 of the EGFR gene, and index medicines gefitinib and erlotinib for the treatment of advanced NSCLC. The related companion diagnostic test is designed to detect mutations in codons 12 and 13 of the K-Ras gene. Other drugs and their companion diagnostic tests that have been recently approved include monoclonal antibodies targeting the programmed cell death protein 1 (PD-1) receptor along with their diagnostic tests that detect PD-L1 expression on tumor cells and immune cells. To identify tissue-agnostic genomic aberrations, the assessment of microsatellite instability (MSI) and its partner reagents have been approved as generic biomarkers for the treatment of relapsed metastatic solid tumors with dMMR. These therapeutic drugs, their indications for clinical use based on tumor genotyping and expression, and temozolomide are listed. Due to the complexity of genomic aberrations in lung cancer, targeted drugs and companion diagnostic tests were finely developed. The limitations and perspectives of lung cancer biomarkers are also examined.

5.3 Colorectal Cancer

Colorectal cancer (CRC) is a poorly understood neoplasia characterised by a long-term multistep process. Cancer is the second leading cause of mortality in developed countries, and CRC is the third most common form of cancer. Although the aetiology is rather preserved globally, the genetic heterogeneity and the microenvironment have led to differences in epidemiology, pathology, clinical behaviour and outcomes in women and men. Recently, a growing body of clinical data has emerged on the use of biomarker/targeted therapy and its successful applications in daily clinical practice for CRC.

Pharmacogenomics represents an irreplaceable tool in order to tailor patients' treatment using an individualized approach based on genetic variations able to predict drugs response and risk of toxicitie 7. Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the western world. The median overall survival (OS) of patients with metastatic CRC (mCRC) has notably increased in the past 20 years, reaching around 30 months in recent phase III clinical trials. Medical and surgical treatment strategies have greatly improved mCRC patients' outcomes over the last years. In particular, the availability of new drugs, development and testing of innovative treatment combinations with different mechanisms of action, and recently breakthrough results in immunotherapy-based approaches have been crucial [10].

Patient outcome and response to treatment can be highly heterogeneous among mCRC patients. Thus, an extensive effort has been directed towards the identification of reliable predictive biomarkers able to tailor anti-cancer treatments to a subset of patients who are most likely to benefit from them. Pharmacogenomics represents an irreplaceable tool to tailor patients' treatment using an individualized approach based on genetic variations able to predict drugs response and risk of toxicities. Generally, the introduction of novel agents represents a stimulus to discover predictive molecular biomarkers able to identify patients' responders to the new therapy. Consequently, the introduction of targeted agents such as anti-epidermal growth factor receptor (EGFR) drugs has prompted a major effort to discover predictive molecular biomarkers for the identification of patients that could benefit from these new drugs.

6 Challenges in Biomarker Discovery

Biomarkers are vital components of the drug development (DD) pathway that advances translational research discoveries into clinical practice [11]. Biomarkers have emerged as essential components guiding patient selection, drug development strategies, and patient monitoring. Over the last decade, there have been significant advances in the discovery and clinical validation of clinically actionable biomarkers, including therapy selection biomarkers, prognostic biomarkers, on-treatment monitoring biomarkers, and toxicity biomarkers. Tumor genetic profiling has become a routine step in the management of patient care. Biomarker-driven drug development is also widely practiced, with the demand for more stringent validation processes. Where fully validated biomarkers are available, they are routinely adopted into clinical practice guidelines. Furthermore, the application of biomarker data has consequently broadened, from traditional tissue-based hunting efforts to population-scale biomarker discovery using bio-specimens such as blood, urine, and saliva.

Despite these advances, much remains to be done to overcome the technical, regulatory, and reimbursement obstacles that have stalled the translation of biomarker research. The most significant challenges relate to the assessment of specimen assessment quality, the presence of bias in the generation of results, and the development of analytic validity standards. Furthermore, it is currently unclear how regulatory authorities will assess the link between a biomarker and the clinical utility of a drug. To support the biomarker development and certification ecosystem, it is critically important to form a network of scientists, industry representatives, policymakers, and government regulators focused on points of interest within this biomarker-focused system. Open forums would create collaborations around the development of comprehensive consensus documents providing the scientific and technical evidence for approaches to assess engagement with specific aspects of the ecosystem.

New challenges arise in reviewing real-world biomarker data, evaluating the link between biomarker attainment and clinical performance in the real world. The rules and guidelines for clinical validation assessment remain unclear, and regulatory authorities are nominally less involved in this process. This gap currently hampers companies' registration and exit strategies to scale-up and commercialize their biomarker products. Consequently, investment is stifled, and promising platforms risk falling into oblivion.

6.1 Technical Challenges

Precision oncology has emerged as a new paradigm for a promising cancer treatment strategy that tailors therapy based on the molecular profile of individual patients' cancers [12]. However, implementation of precision oncology into clinical practice faces significant technical challenges, including limited access to tumor molecular profiling, bioinformatics pipeline delays, multiplexed assay validation, and standardization for tissue-based analytical methods [13]. This delayed delivery of actionable results to oncologists can limit the potential of precision oncology in terms of worthy impact on clinical outcomes. The costly nature of genomic profiling and tumor molecular

characterization represents another key issue for implementation of precision oncology outside of major cancer centers or dedicated academic institutions. Despite important technological advances over the past few years in massive parallel sequencing and molecular profiling technologies, tumor molecular profiles have generally been obtained as static snapshots in time, which do not consider spatiotemporal molecular heterogeneity. These technical barriers should be addressed to accelerate the transition in implementation of precision oncology and other personalized cancer medicine treatments.

In early 2023, a consortium of non-profit organizations formed a collaborative group called 'Benchmarking a Next Generation Molecular Tumor Board' (NMTB) to test low-cost, clinically permissible and lady-accessible platforms that allow community institutions to engage on par with major cancer centers. One solution for implementation of precision oncology at scale and investment return will be considered across limited access cancer care institutions without full-fledged genomic information and analytic capabilities. To minimize diagnostic delivery delays and maximize impact on therapy planning, real-time molecular profiling using liquid biopsies will be discussed together with standard operating procedure recommendations. For more rare mutation variants, feasibility studies will allow testing whether patient tumor samples/protocols can be flexed to real-time capacity when they are sent/represented to major cancer centers. Bioinformatics, data sharing, and data governance will also represent key challenges of this large-scale analysis integrating complex multi-layered datasets.

Two-phase launches are planned over the next 2-3 years to test/provide supporting evidence for these real-world solutions in community non-profit multi-institutional collaborations. The first phase will analyze tumour samples/planning data from recently diagnosed patients at population-based cancer screening programs who are referred to precision oncology/molecular tumor boards protocols. In the second phase, the platform will be scaled to accommodate multiplexed body fluid profiling/regulatory networks. Implementing these solutions would allow individual patients to receive state-of-the-art personalized oncology care at affordable and compensable costs.

6.2 *Ethical Considerations*

The implementation of pharmacogenomic testing could lead to a situation in clinical practice where information about an individual's disease could be revealed to third parties. It is expected that such information would not only reveal a current disease, but also about the consequences of the information concerning the candidate disease, namely discrimination (discriminatory pricing, ineligibility for employment and insurance) [14]. Weighty efforts should be directed towards alleviating this concern regarding privacy and confidentiality of employment and insurance coverage decisions that may be affected by predicted drug safety in the past twenty or more years, a find motivated by the enormous costs of the human genome project. Provisions were provided in the 2008 Genetic Information Nondiscrimination Act prohibiting discrimination based on genetic information in health insurance and employment. Considerable progress has been made, with substantial scholarly contribution, in the last decade on how to assure the confidentiality of genetic data collected for research purposes and by medical professionals.

It would be of help to consider the more general ethical, legal, and social implications of genetic tests in attempting to alleviate concerns. However, most discussions on these issues, notably in the United States, make few distinctions between pharmacogenomic biomarkers and genetic tests predicting disease susceptibility. It would seem reasonable and appropriate that consent for pharmacogenomic biomarker tests, when used according to the consensus provided above or in a manner similar to that, should not be treated with the same extent of scrutiny, deliberation, and regulation as genetic testing for disease susceptibility. Greater specificity would in turn be needed to reassure, ethically, legally, and socially, that implementation of pharmacogenomic tests is sound.

A common concern with respect to the clinical implementation of pharmacogenomic biomarkers is social. An important branch of the social issues, often cited and articulated, is at the level of individual patients: an individual patient of lower socioeconomic status in various aspects (education, income, and the like) could find that he/she is precluded from obtaining potentially beneficial pharmacogenomic test information that a patient of higher status could take advantage of. It is widely agreed that such disparity runs counter to basic social fairness and justice [15].

6.3 *Regulatory Hurdles*

Despite the perceived promise of pharmacogenomics, there are limitations and hurdles that may hinder the translation of pharmacogenomic research into practice. The regulatory framework governing drugs and diagnostics must be adapted to accommodate the unique features of drugs and diagnostics along the continuum of drug development and clinical practice. Adaptive regulatory frameworks are now being designed for pharmacogenomics, and the views expressed in this article on how to navigate the regulatory hurdle could inform best practices in other areas of personalized medicine. It is important to acknowledge that as a disruptive innovation, the transition from an underdeveloped niche to mass-market production and widespread utilization continues to be fraught with uncertainty, and implementation challenges abound as the science, technology, and

marketplace continue to evolve.

Pharmacogenomics can be thought of in terms of at least four key steps, similar to any other drug discovery and diagnostic development process. As with other biomarkers before them, pharmacogenomic biomarkers begin with pre-commercialization, discovery, and development phases. After sufficient data has been collected on safety and clinical validity, the biomarker sponsor may enter the regulatory compliance phase, seeking to prove that the biomarker tests and drug are safe, effective, and in compliance with applicable regulations. FDA approval of biomarker tests and drugs results in the finalized development phase and allows commercialization. After the biomarker test and/or drug has been used in clinical practice for some time, the health care system evaluation phase may assess the new test/drug's health technology assessment (HTA), such as coverage under payment systems, and reinsurance or formulary inclusion under third-party payer systems [16].

7 Clinical Implementation of Pharmacogenomics

Genetic differences between individuals affect how anticancer drugs are metabolized and responded to, influencing drug efficacy and toxicity. Germline variations in pharmacogenes are key factors behind this variability. The discovery of mutation-guided markers (MGMs), combined with affordable genotyping, enables the development of predictive and safety focused pharmacogenomic tests.

However, integrating these tests into clinical practice is complex and requires a structured method. Key steps include: defining test suitability criteria, test design, validation methods, and ethical considerations like cost distribution. The decision to follow strict or flexible guidelines affects how quickly a test can be adopted and its broader clinical legitimacy.

The implementation process should be cautious, following steps used for introducing other lab tests. Historical delays in adopting clinically valuable tests highlight the importance of regulation. Although enthusiasm around new tests may fade over time, there remains a risk of overuse based on premature optimism, or underuse due to hesitancyboth of which carry clinical and legal implications. Properly balancing innovation with regulation is essential for safe and effective use of pharmacogenomic testing.

7.1 Integration into Clinical Practice

The introduction of targeted therapy has greatly improved the efficacy of anticancer treatments. However, it is also true that a high proportion of patients are exposed to treatments that have little or no chance of being efficacious, potentially compromising their safety. There can be various reasons for this. First, most currently used anticancer drugs are not used in a personalized setting and are prescribed based solely on the histopathological characterization of the tumor. In general, it is reasonable to assume that only a subset of patients has tumors that will respond to the agent to be prescribed. Second, most anticancer drugs target a single alteration. Therefore, the presence of an off-target alteration in the tumor can confer resistance to such treatment. Third, the presence of molecular genetic alterations associated with toxicity can be missed, increasing the chances of adverse events [17].

In the past two decades, the effort to understand the genetic drivers of cancer has culminated in accelerating sequencing and profiling of tumors. Whole-genome sequencing, whole-exome sequencing, and genome-wide profiling of RNA transcripts, copy number alterations, and methylation have provided an unprecedented repertoire of genetic alterations in cancer. In addition, a plethora of targeted anticancer agents has been developed, most of them already in clinical use. The concept of personalized cancer therapy, or treatment that takes the molecular characterization of the tumor into account, has emerged, wherein the tumors of patients are characterized using an integrative genomic approach and then used to select treatment and predict therapeutic response and adverse events.

Despite the extreme success of personalized cancer therapy programs in the research setting, few have been implemented in the clinic. To implement this model in the clinic, hospitals must invest a substantial number of resources in various aspects. It is crucial to strike a balance between the need to interpret large and complex data and the necessity to get timely results that are easy to communicate to oncologists and patients. In order to succeed, the following points need to be taken into consideration. Efforts must be made to anticipate the oncoming data flood and to have adequate bioinformatics resources and infrastructure in place to support data processing, interpretation, and visualization. Choosing the right platforms is of paramount importance, as they must address both clinical throughput and assay precision, reliability, and reproducibility. Assay sensitivity must be optimized for an appropriate tumor content in order to facilitate downstream bioinformatics and clinical validation of results [15].

7.2 Patient Education and Consent

As precision medicine efforts become widespread, with pharmacogenomic tests moving to the clinical realm for major and incidental findings, understanding patient education and consent processes for these tests is critical. Pharmacogenomics is the study of how genes affect a person's response to drugs. These tests can analyze a person's DNA to identify variants that can help guide medication efficacy and safety. This assessment's purpose is to provide a snapshot of the current status of patient education, informed consent ahead of pharmacogenomic

testing, and related practices. 200 health care professionals and researchers participated in an anonymous, online survey regarding pharmacogenomic testing patient education, informed consent, and related practices [18]. To date, few studies have examined the pharmacogenomic patient education and consent practices of health care professionals. This assessment reveals significant variability in the pre-test education and consent processes and practices of health care professionals performing pharmacogenomic testing. However, most studies measured the clinical use of pharmacogenomic testing or their patient perceptions. Evidence-based guidelines are needed for pre-test patient education and informed consent processes and practices for pharmacogenomic testing, as exist for other tests. There is a need for studies to guide health care professionals caring for adult and other populations undergoing pharmacogenomic testing.

Pharmacogenomic testing can reveal clinically relevant, actionable genetic information that can be used to guide medication treatment for patients with mental illness and those on medication regimens more broadly. Many health care professionals, other than genetic specialists, are tasked with discussing these results with patients and obtaining consent for pharmacogenomic testing. Informed consent for medical tests is complex, and the patient education and consent process for pharmacogenomic testing is nuanced and growing, necessitating guidance for health care professionals currently tasked with this role. The results of this assessment provide a current snapshot of relevant practices and the point of view of health care professionals and other experts using pharmacogenomic testing as clinical tools.

8 Impact of Pharmacogenomics on Treatment Outcomes

Over the last quarter-century, profound advances in our understanding of the human genome and, more recently, of the epigenome have allowed us to define new causes of inter-individual differences in pharmacological treatment outcomes. The most important discoveries include identification of genetic defects underlying the loss-of-function phenotypes for the majority of the drug-metabolizing enzymes, transporters, receptors and targets [4]. Furthermore, there has been an explosion of discoveries of genetic variants that influence gene expression levels, as a result of which many medications can be shown to be more effective or more toxic in certain genotypes, and probably also less effective or less toxic in other genotypes. While pharmacogenomic tests are already in use for a number of well-characterized polymorphic genes, screening for genetic variants that impact pharmacotherapy is primarily restricted to the screening of a few defined genes, suggesting that there is significant potential for in-house development of tests for a wider range of variants thought to impact drug therapy. The advent of epigenetic approaches to discover novel pharmacogenomic biomarkers is still in its infancy but holds considerable promise.

Pharmacogenomic biomarkers can be classified according to structures, types and functions – i.e. DNA/RNA, mRNA, protein and metabolite biomarkers, inherited genetic, acquired genetic, non-genetic markers, and risk/diagnostic/prognostic/monitoring therapeutic efficacy biomarkers. This broad definition reflects that the detection of these biomarkers is a prerequisite to drug development but does not guarantee understanding of their functions in treatment outcome, as illustrated by the Her2 marker in breast cancer therapy with trastuzumab. The identification of a valid pharmacogenomic marker requires multiple considerations, including the biomarkers' utility to predict treatment outcome, consistency across studies, generalizability across populations and clinical contexts, the mechanism(s) by which it affects treatment outcome, and the knowledge gap regarding unvalidated or poorly characterized biomarkers, which have led to treatment resistance in some patients.

8.1 Improved Efficacy

The recent rise in pharmaceutical Research & Development (R&D) costs and the decline in the number of approved drugs have long called for the need to improve drug development efficiency. Approaches based on pharmacogenomics (PGx) are expected to optimize the efficacy and safety profile of drugs based on individual genome information. The practical application of PGx is a personalized approach that uses biomarkers in clinical trials. There are several drugs for which the patient enrichment biomarkers specified by PGx are listed on the drug label. Examples include crizotinib and dabrafenib. Crizotinib is indicated for the treatment of adult patients with metastatic NSCLC whose tumors are ALK or ROS1-positive. Dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation. The recent emergence of anticancer drugs with innovative mechanisms of action has significantly changed new drug development. Immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors, have dramatically improved the prognosis of patients with cancer. A previous study analyzing FDA-approved anticancer drugs found that the adoption of personalized strategies is associated with improved efficacy. Studies on the impact of personalized strategies on drug development showed that phase transition rates were higher for products using patient enrichment biomarkers. Personalized strategies were associated with higher median response rates and longer median progression-free survival in phase I and II trials. Companies do not unconditionally apply personalization strategies to all drugs. Strategies that seek competitive advantages of a drug other than its high efficacy may also be reasonable in certain therapeutic areas.

In this study, we investigated the adoption of personalized strategies in recent pivotal and/or phase III trials of anticancer drugs approved in the US for the treatment of NSCLC. The application of personalized medicine (i.e., patient selection by biomarker) has been pursued. We examined the relationship between personalized strategies and the effect size in these trials [19].

8.2 Reduced Adverse Effects

During the past two decades of clinical implementation of pharmacogenomics in oncology, the focus has been to improve treatment efficacy and reduce the adverse effects of cancer therapy. Translating pharmacogenomic discoveries into potential benefits for cancer treatment is being promoted by multiple stakeholders including the pharmaceutical industry, clinical laboratories, clinical practice guideline developers, academic researchers, advocacy groups, and governmental regulatory agencies. There is growing evidence to suggest that incorporation of pharmacogenomics in clinical oncology leads to successful risk stratification for the occurrence of adverse drug reactions (ADRs) and improved overall treatment tolerability and patient outcomes. These findings were recently summarized in two large systematic reviews published in The Lancet Oncology [20].

Discovery of pharmacogenomic variants associated with ADRs is critically important to inform the clinical product labeling for the development of companion diagnostics designed to guide drug therapy for patients. The recent countdown paper frames the issue of implementation into health-care practice in terms of the key challenges ahead in patient care, technology, regulation and policy, governance, and education, and discusses potential solutions. In particular, application of the current clinical products aimed at improving treatment safety require careful evaluation of clinical utility and health impact, as well as achievable short-term wins. Nevertheless, the scientific advances and research progress made in this area have set the stage for further improving cancer patient care through the incorporation of pharmacogenomics into clinical oncology.

9 Future Directions in Pharmacogenomics

Many challenges await pharmacogenomics. The translation of pharmacogenomics into clinical practice has been slow in cancer treatment compared with other fields of medicine, such as pharmacotherapy for HIV infection. HIV protease inhibitors serve as an example of how, at the very beginning of treatment, genetic tests were used to create a "virtual patient," allowing scientists to predict, based only on a patient's host-response genes and HIV viral genome, the ideal combination of viral protease-inhibitor drugs that would be both effective and have minimal side effects. One large pharmaceutical company was cradled, while another went bankrupt. Now, HIV protease inhibitors are the standard of care for patients, saving millions of lives [21]. In 2010, the report suggested that pharmacogenomics will lead to the same generations of drugs approved, rapidly replacing less effective and toxic chemotherapeutic agents with more effective targeted drugs based on genetic tests. Unfortunately, faced with the issues of data explosion and complex interpretation right at the start of this era, the promise of personalized cancer therapy remains years from application [14]. As genome-wide association studies have proliferated, basic scientists have discovered genes affecting drug response, even validated by re-analyses of patients who had a drug failure and the complete "plateau of normality." However, the correlation has many caveats: the same gene can cause resistance in one model but sensitivity in another; model systems poorly simulate the drug-effect time frame and complexity of the in vivo environment; and available data are of low quality and limited in scope and population size. Unforeseen follow-up genetic changes invariably arise during the time to perfect the model. Thus, while basic science progresses in describing drug response, at the other end, efforts to introduce companion drugs to the clinics still lag, waiting on reconstruction and verification of the complex and poorly understood processes governing pharmacogenomics by translational scientists using more imperfect data. Even after successful clinical trials, only one out of the ten top new drugs are predicted to break even; thus, substantial interests in patent expiration, off-label use, generic drugs, and unnecessary consumption, coupled with doctor fears of lawsuits and drug-company misinterpretation and misapplication of pharmacogenomics data, likely spur resistance to change.

9.1 Emerging Technologies

Next-generation sequencing (NGS) has driven progress in genomics but remains limited in clinical use due to challenges in assay validation and platform reliability. A test validated on one platform may not work reliably on another. For example, copy number variation detection is rarely used in Japan after its supporting fluidics system was discontinued. Although many local facilities develop NGS-based techniques, these often face regulatory resistance. A notable success is the clonal evaluation test in myeloma, which tracks treatment response based on mutation burden. Biomarkers with strong evidence can be rapidly interpreted into tests, like real-time PCR for lung cancer. However, tests lacking validation remain clinically unusable.

Nano-crystal semiconductors offer promise for next-gen optoelectronics, but poor stability has limited commercial use. Advances in ligand exchange in hybrid perovskites have improved air and heat resistance. Meanwhile, non-toxic colloidal Nano-crystals with rigid lattice structures and low trap densities show potential for commercial use. Integration into low-cost, multifunctional sensors is

underway, with AI-driven design accelerating the development of new Nano-crystal systems for both research and application [22].

9.2 Personalized Medicine Initiatives

Oncology remains the leading field for preemptive pharmacogenomic applications, with extensive research on biomarkers—over 268,000 PubMed-indexed publications—covering genomic, epigenomic, and other molecular variants. Germline mutations (e.g., DPYD, TPMT, UGT1A1) influence chemotherapy pharmacokinetics, while somatic mutations enable pathway-specific targeted therapies, such as EGFR, BRAF, and ERBB2 inhibitors. Whole genome sequencing is increasingly used to individualize cancer treatment beyond common mutations. Current efforts focus on predicting responses to small molecules, with emerging needs to identify biomarkers for biologics, such as PD-1 inhibitors like nivolumab. Despite its survival benefit in melanoma, nivolumab shows limited response rates (20–30%), with underlying resistance mechanisms still unclear [4].

One instrument to support the application of genetic variations in the clinics are pharmacogenomic drug labels. These labels are prepared by the drug manufacturers and submitted for approval to the responsible regulatory agency. Where applicable, they recommend the genotyping of specific genes or variants to guide drug and dose selection, predict treatment outcomes or adverse reactions, or inform about potential effects on drug-drug interactions. A prerequisite for the issuance of the labels is publication of an appropriate number (typically more than 2) of adequately designed and well conducted studies in the peer-reviewed literature on patients receiving the drug in question. Subsequently, several investment funds have become available to support such initiatives. Some efforts have aimed at creating public data on genetic variants affecting drug metabolism, response and toxicity that would be useful for individual patients and their physicians.

10 The Role of Healthcare Providers

Implementing pharmacogenomics in clinical care requires coordinated efforts from multidisciplinary healthcare providers. While some clinical settings have integrated pharmacogenomics, most health systems face barriers such as regulations, reimbursement, EHR limitations, education gaps, and workflow integration. Health care providers—including clinicians, pharmacists, lab staff, IT, and policy experts must address these challenges while managing ethical, legal, and operational concerns. Despite these obstacles, successful collaborations, like the 1000 Genomes Project and ASCO's Quality Oncology Practice Initiative, demonstrate that multi-disciplinary approaches can help overcome implementation gaps. Continued cross-sector collaboration is essential to fully understand the benefits of pharmacogenomics in clinical practice.

10.1 Oncologists

Oncologists have traditionally been responsible for the overall management of cancer patients, including treatment decisions and prescribing of systemic therapies. Checklists with prescriptive recommendations for patients have been made clinically available regarding the use of well-established, evidence-based predictive biomarkers, including mainly tissue-based assessments, and just recently blood-based assays, to guide treatment decisions for the most common tumor types. In practice, however, the quality assurance of these service tests used by physicians to select appropriate treatments can be variable, and pre-analytical issues or inter- and intra-technical variability in performance such as turnaround time, sensitivity, specificity, and reproducibility can lead to pivotal treatment decisions that are based on suboptimal results, causing patients physical hardships or unnecessary expense [4].

The growing interest in targeted therapies has led to the adoption of complex biomarkers in advanced drug development. These pharmacogenomic tests, often provided by a limited number of global companies, are frequently updated and integrated into expansive networks with intricate business models. Implementing such tests involves establishing testing infrastructure, workflows, and operational standards, which adds to the complexity. A significant challenge remains in equipping clinicians to interpret test results that may seem to override or narrow their clinical judgment.

10.2 Pharmacists

Pharmacogenomics (PGx) can impact the following professional practice areas for pharmacist: assessing a patient's PGx profile affecting their therapy; evaluating PGx test results; providing patient education about a PGx test, its results, and implications for therapy; communicating with other health care professionals about a patient PGx profile and possible implications for therapy; making or modifying medication therapy as necessary based on a patient's PGx profile and test results; and monitoring a patient's response to therapy. While there are many best practice guidelines and tools available, implementation of these in routine practice remains a challenge. A responsive PGx consultation service is presented, illustrating the role of a pharmacist as part of this service, and highlighting the challenges and potential solutions for prescribers [23].

Pharmacists can utilize available evidence to inform and make their contributions to the development and implementation of PGx consultation services in routine clinical practice. This pharmacy-led proactive PGx consult

service is evaluated, highlighting consults completed by both pharmacy students and practicing pharmacists, their activities, workflows, and challenges experienced. This service provides a successful model for multidisciplinary clinicians or groups interested in building their own PGx consult services.

Population pharmacokinetics of voriconazole was investigated in children and adolescents with neuroblastoma. A large interindividual variability was found in voriconazole clearance and volume of distribution, which was accounted for by body surface area while accounting for body size in adolescents. This study highlights the importance of weighing considerations during the early treatment phase using the dosing guidelines, further confirming adverse drug events. Targeting TDM during the early treatment phase would improve the safety while keeping the treatment duration.

Oncologists can assist in the implementation of PGx by developing a familiarity with laboratory processes in pharmacy, knowing what information is derived from tests and available to physicians, and communicating ways in which this information can be used to assist in treatment. Oncologists cannot be responsible for the oversight or interpretation of results from various testing vendors; however, they can use their knowledge to request additional information from these vendors to better guide their treatment decisions.

10.3 Genetic Counselors

Due to the genotypic advancement of the Genome Sequencing across the globe, there is a great need for the implementation of Genetic Counselors to facilitate it in the clinics. The clinical implementation of pharmacogenomics calls for workforce education in several pharmacological areas, which places a heavy burden on the point-of-care providers. On similar grounds, the integration of Medical Geneticists to the clinics providing Genetic Testing services is significantly limited in the existing healthcare systems. Therefore, the need for additional trained workforce is greater than ever before. The Genetic Counselor workforce can be utilized as an alternative to the Medical Geneticist and as an important part of the pharmacogenomics education in the clinics.

Pharmacogenomics is the study of inherited genetic variations that influence the metabolism and effect of medications, as well as the development and course of disease. It provides conditions tailored to the individual's characteristics. Pharmacogenomic markers can help identify patients less likely to respond to a particular therapy or more likely to experience an adverse effect from a standard of care regimen. These markers can take the form of a chromosomal mutation, single nucleotide polymorphism, genome deletion, or copy number variation. The development of genetic tests for several of these biomarkers is being actively pursued by pharmaceutical companies in the hopes of increasing drug development success rates and drug prescribing accuracy.

Genetic counselors play a vital role in pharmacogenomics through test interpretation, education, and psychological support. They assist clinicians by explaining pharmacogenomic test results, guiding test selection, and interpreting relevant evidence. A key responsibility is providing unbiased education to counter misinformation. Counselors also inform patients about medication use, adverse drug reactions, and phenotype-related behaviors such as smoking. Their role may further extend to supporting algorithm-based decision-making and offering psychological counseling related to test outcomes, positioning them as [24].

11 Patient-Centric Approaches in Pharmacogenomics

Over the past few decades, the Interdisciplinary Center for Cognitive Irregularity has focused on adapting Theragnostics Analysis (TA) technology for clinical studies. Theragnostics tests identify biological factors in patient tissues that may indicate response to target therapies. Referral of eligible patients to Theragnostics studies from a broader population undergoing standard therapy adds a layer of complexity to the development and application of targeted drugs [1]. In the first adaptation of these trials for a clinical setting, the central question is whether Theragnostics tests can be successfully implemented to improve clinical outcomes in typical oncology practice, which has lower response rates than clinical trials. All elements of the testing process, including accessibility, compliance, and outcomes, must be evaluated in detail to inform further refinement and broader application of this technology. Four questions explored aspects of patient care and specialty practice that impact or are impacted by Theragnostics tests: Is the test accessible. Does the test get done. What do results mean for clinicians and patients. Does the test make a difference. For any patient, indications for genetic testing fluctuate depending on treatment options. For a positive decision (suitable patient) in the first trial, a negative decision with a site-specific test retakes the initial test yet shifts it to the negative (unsuitable patient). The turnaround times of Theragnostics tests or alternative testing pathways also affect patient care decisions. Optimal conditions for early treatment with target therapy have not been determined [14]. In the Theragnostics test process, there is a 25-30% decline rate of eligible patients between referral and consultation. For patients who consult, there is a 38% decline rate of compliant patients between the first consultation and testing, with a 76% decline rate for those not completing round-one testing. The parallel study reveals that only half of the patients who test experience something unanticipated.

12 Ethical and Social Implications

Ethical and social questions that arise from pharmacogenomic advances, especially those that are currently relevant for avoiding known drug side effects and correctly choosing drugs in specific tumor types, are timely, considering that pharmacogenomics is a subject of great current importance. It has been proposed that the entire population be genotyped for polymorphisms of drug metabolizing enzymes, as a measure that could prevent a large number of serious and adverse drug reactions. In the coming years, focal pharmacological treatment based on the disease genomic is likely to increase enormously. Nevertheless, the moment polygenic tests for major clinical disorders can be implemented remains a great source of debate. Political and ethical issues arise about consent for the large-scale acquisition of genomic/pharmacogenomic data; about public vs, private ownership of genomic research results; about drug efficacy and safety testing for drugs used in rare genomic indications; and about accessibility to treatment based on costly research applicable to relatively few patients [25]. These issues pertain in particular to drugs for complex disorders and side effect prediction in medications used for common clinical disorders. The theory and manner in which pharmacogenic research can be used to develop drugs and avoid drug side effects should be given, as a background with particular emphasis on psychiatric disorders. Significantly, the pharmacogenomics of psychiatric disorders presents unique and serious challenges, both because of the complexity of the underlying science and the subjectivity of treatment. However, treatments are inordinately expensive, complex, and pose risk of disturbance of a complex bio/psychological equilibrium. Thus, psychiatric pharmacogenomics provides unique opportunities and challenges. A permanent special committee on pharmacogenomics and policy need to be constituted to address these issues on a long-term basis [26].

12.1 Access to Testing

As pharmacogenomic tests enter the clinical arena, understanding patients' access to tests in the context of health care systems is crucial [27]. A quality framework for cancer care, the Access to Testing model provides a multidimensional perspective to conceptualize and examine access to pharmacogenomic testing. System policies and regulations, institutional policies, system resources, patient-level factors, provider-level factors, and inter-provider factors were key themes that shaped access to pharmacogenomic testing from both providers' and patients' perspectives. As precision medicines in oncology proliferate, health care systems worldwide will need to undertake extensive changes to achieve equity in access to testing.

Already in clinical practice, pharmacogenomic tests inform more than 150 medications in cancer and non-cancer therapeutic areas. In precision oncology, such tests identify patients with targetable biomarkers for approved targeted therapies to improve treatment efficacy. Current broad access to genome sequencing technologies in research and commercial settings provides hopes for patient recruitment for clinical trials of novel genomic-based drugs, but anticipated academic and biotechnology investments over next few years haven't yet led to more precision medicines entering the clinical pipeline. Meanwhile, there is an increasing number of guideline-recommended pharmacogenomic tests to enable safer and effective use of cancer treatment. Among genomic tests for drugs, FDA-approved pharmacogenomic tests in oncology are the most common and account for more than 80% of tests with sufficient evidence for clinical utility. The NCCN guidelines recommend pharmacogenomic tests to inform a growing number of medications for many types of cancers because sufficient evidence of benefits has been established. Access to the tests may affect subsequent treatment decisions about drugs and have far-reaching effects on patient health outcomes.

12.2 Discrimination Concerns

Each step towards personalized or targeted medicine has the potential to further inequities in access to health care. Health care is a scarce resource, and any test or treatment discovery therefore raises the questions of who will be tested or treated and of who will bear the costs of testing and treatment. The concern is not simply one of the equitable distribution of resources: unfair discrimination could arise both through outright exclusion and through biases in group or individual risk predictions, increasing the likelihood that certain populations are excluded or misidentified. At the same time, as this discovery pipeline moves from case-control studies to population screening or treatment in individual clinics, the introduction of such biomedical technologies into health care systems raises ethical questions on whether the tests and technologies are being introduced equitably and for demonstrated efficacy and safety reasons [28].

Beyond legal issues, the use or exclusion of individuals from pharmacogenomic testing on non-medical grounds raises ethical concerns, particularly regarding potential harm and inequities in resource distribution. These concerns highlight systemic disparities, especially as new health technologies tend to benefit already well-researched populations. Such inequities include limited access to data-driven benefits, exclusion from evidence-based therapies, and missed economic opportunities for underrepresented groups. These non-medical factors may lead to unequal access to personalized medicine, producing group- or individual-level disadvantages unrelated to biological variability Health systems are complex bio-social systems exhibiting both normative and behavioral institutions.

Normative institutions governing decision-making therein introduce both inequities in the distribution of access to health care and paradigms or frames of action for guidance on resolving inequities. Decisions helping to minimize inequities can lead to negative feedback loops reinforcing inequities.

13 Global Perspectives on Pharmacogenomics

Pharmacogenomics is a field that emerged from the effort to exploit the increasing knowledge on the human genome to tailor drug selection and dosing to the patient's genetic features. Growing evidence has shown that molecular variations can affect drug metabolism, transport or targets, and can influence the risk of either efficacy failure or toxicity. These polymorphisms were partly studied by a pharmacogenetics approach that provided the basis for understanding the impact of allelic variants on the biotransformation and response to drugs. The above-mentioned variations affecting pharmacokinetics and pharmacodynamics can be detected at genomic level, and by indication, the tests can be performed on metabolically active tissues or biofluids. Yet, while extensive efforts have been undertaken to introduce pharmacogenomic testing into routine clinical practice, the uptake of pharmacogenomics in public health remains limited.

The variability in clinical response to standard therapeutic dosage regimens was first reported over fifty years ago. The first associations of monogenic polymorphisms with the individual variability of the metabolism, transport or targets of drugs came in quick succession after the introduction of the very first drugs. The demonstration of pharmacogenomic contributor(s) variants to the individual variability of drugs' metabolism, transport or target impelled the vision of personalized drug therapy. This holds the premise that a large portion of the interindividual variability in the pharmacokinetics and/or pharmacodynamics of the drug is genetically determined.

Accumulating evidence, including real-world cases, supports the clinical integration of pharmacogenomic-guided therapy in the near future. However, despite growing scientific and clinical acceptance, fully achieving personalized medicine remains a long-term goal. The development and implementation of pharmacogenomic tests follow a staged process: initial biomarker discovery, replication of drug-gene associations, physiologically based modeling for regulatory approval of companion diagnostics, randomized clinical trials to assess clinical impact, cost-effectiveness studies, and stakeholder engagement for broader adoption.

13.1 Variability in Implementation

Variability in clinical response to standard therapeutic dosage regimens of drugs was reported in the 1950s, and initial focus was placed on population studies to identify covariates affecting drugs' pharmacokinetics and pharmacodynamics. These variations are often associated with inherited gene-gene or gene-environment interactions [4]. Since then, the association between a class of monogenic polymorphisms and the variations of drugs' metabolism, transport, or target was identified. Although it is now well-accepted that pharmacogenomic-guided drug therapy for patients is based on the premise that a large portion of the interindividual variability in drug response is genetically determined and that implementation of these tools in the clinical setting will provide substantial societal benefits, most clinicians still agree that personalized therapy in the complicated form of therapeutic regimens tailored to an individual's genetic profile remains some years away [14]. There are also different perspectives among scientists, clinicians, and the public about the readiness for pharmacogenomics. The current perception is that despite the tremendous efforts put into the underlying science on pharmacogenomic biomarkers and the development of drug-genetic tests over the last 20 years, few of these tests are widely used from the standpoint of medical practice [29].

Broadly speaking, the development and implementation pathways for pharmacogenomic tests consist of the following stages: discovery of pharmacogenomic biomarkers in well-controlled studies followed by validation in independent, well-controlled studies; replication of drug-gene(s) association and demonstration of utility in at-risk patients and well-controlled studies; development and regulatory approval of a companion-diagnostic pharmacogenomic test; assessing the clinical impact and cost-effectiveness of the pharmacogenomic biomarkers; and involvement of all stakeholders in clinical implementation. Lessons learned in making pharmacogenomic-guided therapy useful to clinicians have identified multiple scientific challenges and a variety of implementation barriers existing within these stages.

13.2 International Guidelines

In recent years, multiple organizations have issued pharmacogenomic guidelines in oncology, largely recommending genetic testing for drug metabolism, transport, and efficacy. However, few guidelines directly influence clinical decision-making at the bedside or meet regulatory standards for clinical laboratory use. These guidelines generally follow the IOM model of evidence collection, drafting, expert review, and validation. Their strength varies by evidence level, with the FDA offering level 1A recommendations. The ESMO/MAP and Canadian consensus include the highest number of drugs, though CPIC guidelines, despite being less detailed, are expanding. A notable gap remains in governmental guidance for certain drugs, possibly due to stricter U.S. regulations following past drug failures [13]. Moving

forward, there is a need to encourage governmental agencies to issue targeted guidelines, starting with vinca alkaloids, and to harmonize existing recommendations to expand drug coverage and consistency [30].

14 Conclusion

With the rapid advancement of pharmacogenomics, this paper reviews the current landscape of pharmacogenomic biomarkers in FDA-approved drugs, emphasizing their role in optimizing drug selection and dosage. It presents an overview of key biomarkers, drug classifications, and mechanisms of action, while also highlighting the increasing demand for pharmacogenomics and personalized medicine in the UAE. The paper discusses future directions, including education, counseling, and regulatory and ethical considerations. Additionally, it addresses challenges such as regulatory oversight, applicability across diverse populations, treatment adherence, and alignment with clinical guidelines. A focused assessment of TKIs explores biomarker prevalence, clinical action ability, drug approval trends, metabolic pathways, and their predictive value for treatment outcomes and adverse reaction.

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