

ARTICLE

# Gene Variation: The Key to Understanding Pharmacogenomics and Drug Response Variability

Jacob Oliver, William Mason\*

Department of Surgery, University of Toronto, Toronto, Ontario, Canada

\*Corresponding author: [Will.mason@uhn.on.ca](mailto:Will.mason@uhn.on.ca)

(Received: 09 March 2020; Revised: 13 May 2020; Accepted: 06 July 2020; Published: 31 July 2020)

## Abstract

Gene variation is pivotal in understanding pharmacogenomics and drug response variability, as genetic differences significantly influence individual reactions to medications. Pharmacogenomics explores how genetic variations impact drug efficacy and toxicity, aiming to tailor medical treatments to each patient's genetic profile. Specific gene variants can affect drug metabolism, transport, and targets, leading to diverse therapeutic outcomes and adverse effects among individuals. Advances in genomic technologies, such as next-generation sequencing, enable comprehensive identification and analysis of these genetic variants. This facilitates the development of personalized medicine approaches, where treatments are optimized based on genetic makeup, improving efficacy and minimizing adverse reactions. Understanding gene variation also aids in identifying biomarkers for predicting drug responses, contributing to more precise and effective healthcare. This abstract underscores the importance of gene variation in pharmacogenomics, highlighting its role in elucidating drug response variability and advancing personalized medicine, ultimately enhancing patient care and therapeutic outcomes.

**Keywords:** Biomarkers; Drug Response; Gene Variation; Genetic Profiling; Personalized Medicine; Pharmacogenomics

**Abbreviations:** ADME: Absorption, distribution, metabolism, and elimination, ELSI: Ethical, Legal, and Social Implications, GWAS: Genome-wide association studies PD: Pharmacokinetics, TPMT: Thiopurine Methyltransferase

## 1. Introduction

Gene variation in our DNA and hereditary material plays a pivotal role in shaping how individuals respond to drugs and therapies. Pharmacogenomics, the study of how genetic factors influence drug response variability, has emerged as a critical field in understanding the complex interplay between our cells' molecular makeup and the efficacy and safety of medications [1, 2].

This article delves into the fundamental principles of pharmacogenomics, exploring how gene variations impact drug metabolism, pharmacokinetics, and pharmacodynamics. We will examine the contributions of genome-wide association studies, single gene variants, and combinatorial approaches in deciphering the genetic underpinnings of drug response variability. Additionally, we will discuss the clinical implementation of pharmacogenomics, technological advancements driving mitochondrial discoveries, and the evolutionary implications of personalized medicine (Fig. 1) [3].

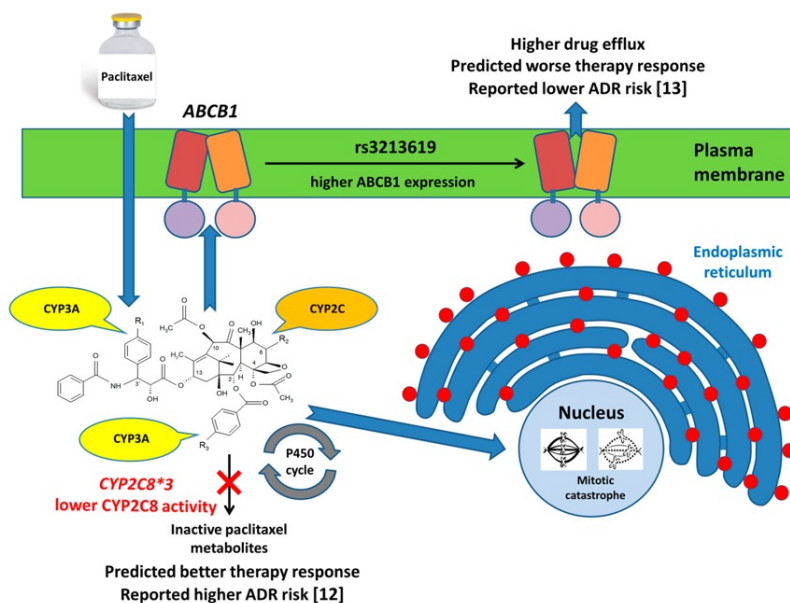


Figure 1. Major functional aspects of ATP-binding cassette.

## 1.1 Genetic Factors in Drug Metabolism

Genetic factors play a crucial role in influencing how individuals metabolize and respond to medications. Pharmacogenetics, the study of how genes affect drug responses, has revealed several key genetic variants that can significantly impact drug metabolism and efficacy [4].

1. **Cytochrome P450 (CYP) Enzymes:** The CYP enzymes are responsible for the majority of phase I drug metabolism. Some notable examples include:
  - **CYP2D6:** This enzyme exhibits the largest phenotypic variation, with individuals classified as poor, intermediate, extensive, or ultrarapid metabolizers. Variations in CYP2D6 can impact the metabolism of 25-30% of drugs, including codeine, paroxetine, tamoxifen, and clozapine.
  - **CYP2C19:** Genetic variants in CYP2C19 can lead to poor, intermediate, or extensive metabolizer phenotypes, affecting the metabolism of drugs like clopidogrel, proton pump inhibitors, and phenytoin.
  - **CYP2C9:** Variants in CYP2C9 can result in reduced enzyme activity, impacting the dosing and response to drugs such as warfarin and phenytoin.
2. **Other Metabolizing Enzymes:**
  - **Thiopurine Methyltransferase (TPMT):** Variations in the TPMT gene can put individuals at high risk of life-threatening bone marrow suppression when treated with standard doses of thiopurine drugs.
  - **UDP Glucuronyltransferases (UGTs):** Genetic variants in UGT enzymes, such as UGT1A1, can influence the metabolism and clearance of drugs like irinotecan and atazanavir.
3. **Population-Specific Genetic Variations:**
  - Frequencies of functional genetic variants can vary significantly across different geographic populations.
  - For example, a study in a Pakistani population found higher prevalence of variant alleles in genes like CYP1A2, CYP2B6, CYP2C19, and CYP3A5, which could impact the metabolism of

various drugs, including docetaxel, bupropion, efavirenz, and anti-tuberculosis drugs.

#### 4. Pharmacokinetic and Pharmacodynamic Effects:

- Genetic factors can influence drug responses through effects on pharmacokinetics (drug metabolism, transport) or pharmacodynamics (drug targets, biological context).
- For instance, warfarin dosing is influenced by genetic polymorphisms in both CYP2C9 (pharmacokinetics) and VKORC1 (pharmacodynamics), allowing for more accurate initial dosing.

The identification of these genetic variants has significant implications for personalized medicine, enabling healthcare providers to optimize drug selection, dosing, and treatment strategies based on an individual's unique genetic profile [5].

## 2. Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (PK) and pharmacodynamics (PD) are two fundamental concepts in pharmacology that play a crucial role in drug development and personalized medicine. PK focuses on how the body processes a drug, including its absorption, distribution, metabolism, and elimination (ADME). Understanding these processes is vital for determining the appropriate dosage and minimizing toxicity [6].

- **Absorption:** The process by which a drug enters the body's circulation from the site of administration.
- **Distribution:** The process of a drug dispersing throughout the body's tissues and blood.
- **Metabolism:** The process of a drug being broken down by the body, often in the liver.
- **Excretion:** The process of the body eliminating the drug or its byproducts, primarily through the kidneys.

Factors such as the first-pass effect, protein binding, and physiological barriers like the blood-brain barrier and placental barrier can significantly impact a drug's PK profile. Additionally, liver and kidney function, as well as age, can alter drug pharmacokinetics (Fig. 2).

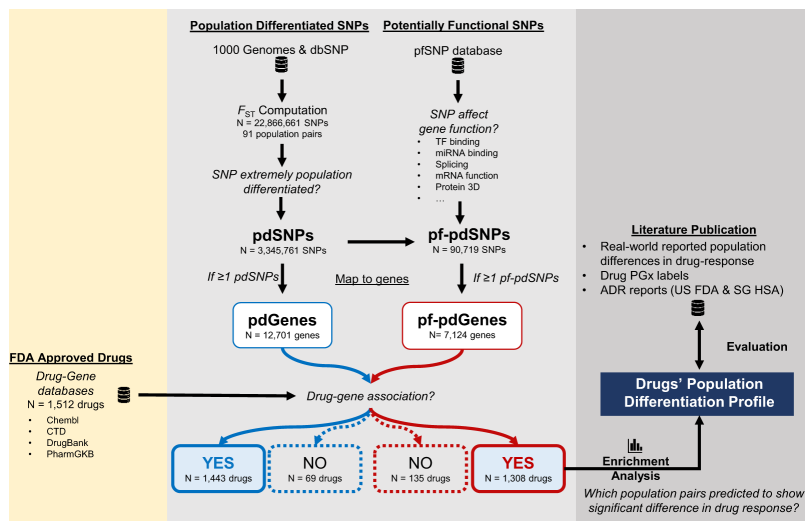


Figure 2. Interrogating the human genome.

On the other hand, PD refers to the effects of drugs in the body and their mechanism of action.

It examines the complex interactions between the drug, the human body, and the target pathogen, aiming to optimize dosing to achieve the desired therapeutic effect. Bioavailability, which is the amount of a drug that reaches systemic circulation and is available to produce an effect, is a key PD parameter [7].

Gene variation can significantly influence both PK and PD, leading to differences in drug efficacy and safety. Commonly studied pharmacogenes in clinical trials and by regulatory agencies like the FDA include CYP2C9, CYP2C19, CYP2D6, DPYD, and TPMT for PK. Understanding the relationship between PK and PD is critical for drug development and approval, contributing to about 25% of the information in a drug's package insert or label.

As given in Table 1, PK/PD analyses involve data management, programming, CDISC dataset creation, noncompartmental PK analysis (NCA), population PK (popPK) analysis, dosing simulations, regulatory submission packages, and nonclinical and clinical ADME study design and interpretation [8, 9].

**Table 1.** PK/PD analyses

| PK/PD Analysis                                | Application                               |
|-----------------------------------------------|-------------------------------------------|
| Characterize drug exposure                    | Determine appropriate dosing              |
| Assess changes in dose requirements           | Estimate absorption and elimination rates |
| Assess bioavailability/bioequivalence         | Characterize variability                  |
| Understand concentration-effect relationships | Establish safety margins and efficacy     |

## 2.1 Genome-Wide Association Studies

Genome-wide association studies (GWAS) provide an unbiased approach for discovering mechanisms and pathways underlying drug responses and toxicities. These studies involve testing hundreds of thousands of genetic variants across many genomes to identify those statistically associated with a specific trait or phenotype related to drug response [20]. Key PGx GWAS findings include identifying actionable genetic variants that guide drug selection and dosage, as well as variants associated with drug toxicities [10]. Some notable examples of PGx GWAS discoveries include:

- Variants in SLCO1B1, CYP2C9, VKORC1, and IL28B associated with drug metabolism, efficacy, and toxicity
- CYP2C19 variants affecting the antiplatelet effect and clinical efficacy of clopidogrel
- VKORC1, CYP2C9, and CYP4F2 variants as major determinants of warfarin dose requirements
- NUDT15 variants linked to thiopurine toxicity

However, challenges limiting PGx GWAS include difficulty obtaining large sample sizes, particularly for adverse drug reactions. The majority of PGx GWAS participants (88% in discovery cohorts) are of European ancestry, limiting the ability to discover population-specific associations. Efforts to accelerate PGx GWAS include establishing large international consortia to study PGx of various drugs, such as the PGRN-RIKEN Global Alliance. More PGx GWAS are needed to identify clinically actionable biomarkers and generate new mechanistic hypotheses, requiring continued collaboration across institutions and countries as explained in Table 2. Emerging technologies like whole exome and genome sequencing are expected to further advance the field of pharmacogenomics [11].

**Table 2.** Challenges and Advantages of GWAS

| Advantages of GWAS                             | Challenges in GWAS                     |
|------------------------------------------------|----------------------------------------|
| Detect small to modest genetic effects         | Need for large sample sizes            |
| Finely localize associated variants            | Bias in variant selection on platforms |
| Gain insights into underlying biology          | Complex drug response phenotypes       |
| Estimate heritability and genetic correlations | Difficulties in study design           |
| Inform drug development                        | Replication and validation of findings |

## 2.2 Single Gene Variants

Early progress in pharmacogenomics came from candidate-gene studies, which investigated the association between specific gene variants and drug response phenotypes. For example, variants in the TPMT gene were found to be associated with thiopurine toxicity, while CYP2D6 variants were linked to codeine response. More recently, large-scale studies have leveraged whole-genome sequencing data to comprehensively investigate pharmacogenomic variants across diverse populations. A study by Zhao et al. analyzed whole-genome sequencing data from 487 central Han Chinese individuals, identifying:

- 2,139 (81.18%) of the 2,635 clinically relevant variants in the PharmGKB database
- 5,723 potentially deleterious variants in 1,316 pharmacogenes, including 1,281 novel variants
- Significant differences in allele frequencies of these variants compared to global populations, highlighting genetic heterogeneity among ethnic groups

**Table 3.** Key findings

| Key Finding            | Description                                                                                                                                                                    |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rare Variants          | Most genetic variants in drug-related genes are very rare (allele frequency < 0.1%)                                                                                            |
| Common Variants        | 43% of drug-related genes have at least one functional variant with allele frequency > 0.1%                                                                                    |
| High CAP Scores        | Genes with the highest cumulative allele probability (CAP) scores include ADME genes like NAT2, CYP2D6, and SLCO1B1, as well as drug target genes like TYR, GABRA4, and F5     |
| Cancer Therapeutics    | 40 out of 163 drug target genes for cancer therapeutics have CAP scores 1%, suggesting a high probability of functional germline variants that could affect treatment response |
| FDA-Approved Drugs     | 43% of the 1,236 FDA-approved drugs analyzed have a 'drug risk probability' (DRP) greater than 1%, indicating they are affected by functional variants in their target genes   |
| Population Differences | There are significant differences in the prevalence of functional variants in drug-related genes across different geographic populations                                       |

The study identified 24 variants with high levels of clinical evidence (PharmGKB levels 1A and 1B), involving genes such as CYP and VKORC1. Additionally, 85 common (>10% allele frequency)

deleterious variants were found to have significantly different allele frequencies compared to other populations. Another study by Schaa *et al.* examined genetic variation in 806 drug-related genes, including 628 known drug targets, using exome data from 60,706 individuals in the ExAC dataset. The key findings as given in Table 3:

These studies highlight the importance of investigating single gene variants in pharmacogenomics, as they can significantly impact drug efficacy, safety, and dosing requirements across diverse populations [12, 13].

### 3. Combinatorial Pharmacogenetics

While single gene variants can provide valuable insights into drug response, many complex traits and drug phenotypes are influenced by the combined effects of multiple genetic factors. Combinatorial pharmacogenetics examines these polygenic interactions, offering a more comprehensive understanding of variability in drug efficacy, dosing, and adverse reactions Figure 3.

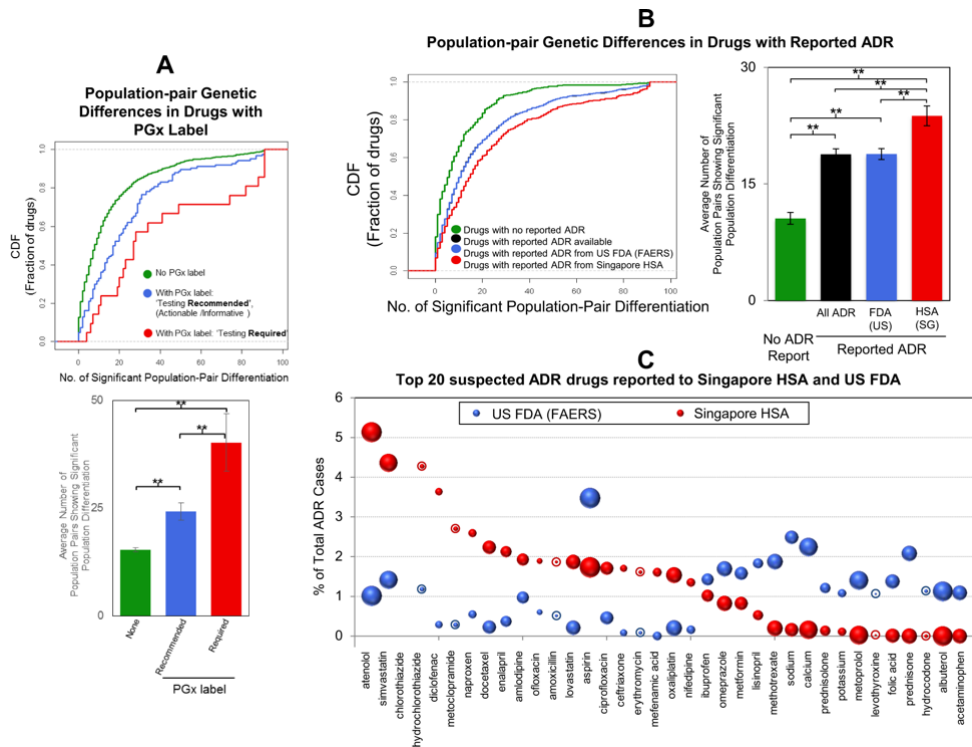


Figure 3. Interrogating the human genome.

A notable example is warfarin, an anticoagulant widely used for the prevention and treatment of thromboembolic disorders. Warfarin dosing is influenced by variants in both the cytochrome P450 enzyme CYP2C9, which affects warfarin metabolism (pharmacokinetics), and the vitamin K epoxide reductase complex subunit 1 (VKORC1) gene, which encodes the target enzyme for warfarin (pharmacodynamics). By considering the combined effects of these genetic factors, algorithms have been developed to predict optimal warfarin dosing, reducing the risk of over- or under-anticoagulation [14, 15].

Similarly, the antiplatelet drug clopidogrel exhibits a complex pharmacogenetic profile. Variants in

the CYP2C19 gene, which is involved in the metabolic activation of clopidogrel, have been associated with decreased platelet inhibition and increased risk of cardiovascular events. However, other genes, such as ABCB1 and CES1, also contribute to clopidogrel response variability as given in Table 4. Recent studies have explored the use of multi-locus genetic risk scores, combining the effects of multiple genetic variants, to better predict clopidogrel efficacy and guide personalized antiplatelet therapy.

**Table 4.** Combinatorial Pharmacogenetic Approach and advantages

| Combinatorial Pharmacogenetic Approach                   | Advantages                                                 |
|----------------------------------------------------------|------------------------------------------------------------|
| Considers multiple genetic factors                       | More accurate prediction of drug response                  |
| Accounts for gene-gene interactions                      | Improved dosing algorithms and treatment strategies        |
| Incorporates pharmacokinetic and pharmacodynamic factors | Potential for reduced adverse events and improved efficacy |
| Utilizes polygenic risk scores or multi-locus models     | Captures the complexity of drug response variability       |

As our understanding of the genetic architecture of drug response continues to evolve, combinatorial pharmacogenetics will play an increasingly important role in optimizing drug therapy and realizing the promise of personalized medicine [16, 17].

### 3.1 Unbiased Approaches

Approaches to identifying genes and variants that modulate drug responses include candidate gene studies, genome-wide association studies (GWAS), and examining genetic variation in biological pathways related to drug action. While candidate gene studies have provided valuable insights, they are limited by their focus on a small number of pre-selected genes. GWAS, on the other hand, offer an unbiased, hypothesis-free approach to discovering novel genetic associations with drug response phenotypes (Fig. 4).

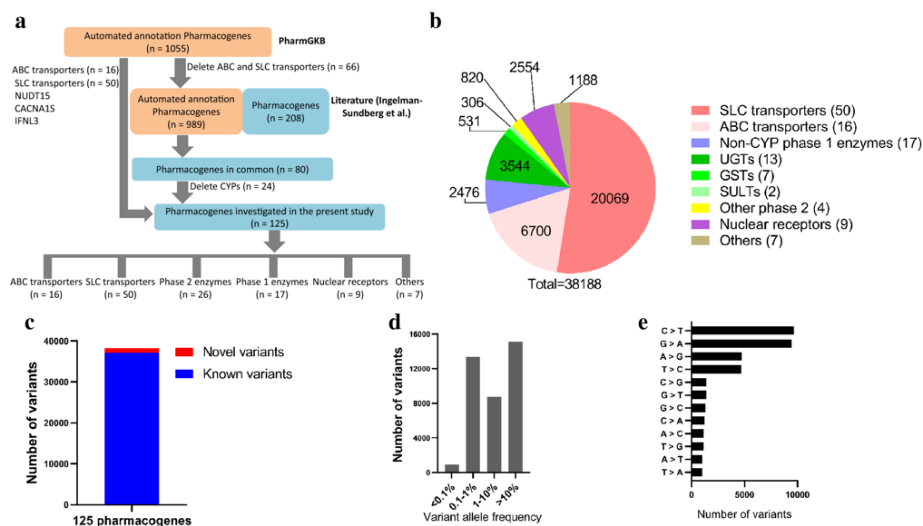


**Figure 4.** Genetic landscape of 125 pharmacogenes

In vitro cell line model systems, such as HapMap and Human Variation Panel lymphoblastoid cell lines, are being used to perform genome-wide pharmacogenomic studies. These models allow for the systematic evaluation of genetic variants across the entire genome, enabling the identification of novel associations that may have been overlooked in candidate gene studies. However, it is important to note that findings from cell line models may not always translate directly to in vivo human responses, and further validation is often required [18, 19].

Whole genome and exome sequencing are emerging as powerful tools in pharmacogenomics, providing a comprehensive view of an individual's genetic variation. These approaches have the potential to uncover rare and novel variants that may contribute to drug response variability. However, the interpretation of the vast amount of data generated by these methods remains a significant challenge. To address this, consortia are working to establish guidelines and best practices for the clinical implementation of whole genome/exome sequencing in pharmacogenomics as shown in Table 5.

**Table 5.** Key findings

| Approach                      | Advantages                                 | Limitations                                              |
|-------------------------------|--------------------------------------------|----------------------------------------------------------|
| Candidate Gene Studies        | Focused investigation of known genes       | Limited scope, may miss novel associations               |
| GWAS                          | Unbiased, hypothesis-free discovery        | Large sample sizes required, may miss rare variants      |
| Pathway Analysis              | Considers biological context               | Relies on existing knowledge, may miss novel mechanisms  |
| Cell Line Models              | Systematic evaluation of genetic variation | Findings may not translate directly to in vivo responses |
| Whole Genome/Exome Sequencing | Comprehensive view of genetic variation    | Data interpretation challenges, high cost                |

As our understanding of the genetic basis of drug response continues to evolve, a combination of these unbiased approaches, along with traditional candidate gene studies and pathway analyses, will be necessary to unravel the complex interplay between genetics and pharmacology. Ongoing collaboration and data sharing among researchers, clinicians, and consortia will be crucial in translating these findings into improved patient care and personalized medicine strategies [20].

## 4. Clinical Implementation

The clinical implementation of pharmacogenomics presents several challenges that need to be addressed for its successful integration into healthcare systems. Here are some key considerations:

- **Ethical, Legal, and Social Implications (ELSI):** Concerns around autonomy, health-technology access disparities, use of special populations in research, and the risk of racial geneticization in pharmaceutical development are among the most significant ELSI issues. Stakeholder communication and engagement, especially with the general public, are crucial for improving access to pharmacogenomics.
- **Education and Adherence:** Inadequate education of healthcare providers, regulators, patients, and the public can lead to irrational use of pharmacogenomic (PGx) testing and treatments. Adherence and compliance issues among both healthcare providers and patients can impact the rational use of PGx.

- **Clinical Guidelines and Infrastructure:** Lack of comprehensive clinical guidelines and health information technology infrastructure are challenges in translating PGx from bench to bedside. Adapting clinical trial protocols to evaluate PGx-based therapies and demonstrating the clinical utility and validity of PGx tests are also important considerations.
- **Regulatory Frameworks and Availability:** Regulatory frameworks need to be updated to accommodate PGx products and companion diagnostics (CDx). The availability of PGx-labeled drugs and CDx is limited due to long approval and registration timelines are explained in Table 6.

Table 6. Regulatory frameworks

| Barrier                    | Description                                                                                                                                                                                                                                                         |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Validation                 | Many significant pharmacogenomic findings are seen in small studies and lack validation in large, well-defined studies.                                                                                                                                             |
| Regulatory Approval        | Regulatory approval is required for in-vitro diagnostic tests to be used clinically, beyond research-use only tests                                                                                                                                                 |
| Test Availability          | Clinicians need to be aware of the availability and how to access approved pharmacogenomic tests, either locally or through centralized labs                                                                                                                        |
| Dosing Recommendations     | Lack of clear dosing recommendations based on pharmacogenomic test results is a major barrier to clinical adoption                                                                                                                                                  |
| Health Records Integration | Integrating pharmacogenomic data into electronic health records and providing decision support could facilitate clinical implementation, but requires availability of approved assays, dosing algorithms, and a system to transfer test results and recommendations |

- **Cost and Reimbursement:** Pricing and high costs of PGx-based therapies and CDx are major concerns, and reimbursement policies and health technology assessments (HTAs) for PGx products are lacking or inadequate.
- **Ongoing Research Needs:** Identifying and validating new pharmacogenomic markers for various medications is an ongoing research need. Increased use of next-generation sequencing technologies and exploration of polygenic risk scores to enrich clinical trials and understand drug response are also areas of active research.

Despite these challenges, the clinical implementation of pharmacogenomics is progressing, with the availability of companion diagnostic tests to identify relevant genetic variants and predict drug metabolism phenotypes. As pharmacogenomic knowledge advances, the clinical use of genetic testing to personalize drug therapy is expected to increase Figure 5.

#### 4.1 Technological Advancements

Pharmacogenomics has undergone a remarkable transformation, evolving from early discoveries of genetic differences affecting drug response and metabolism to the current focus on 'pharmacogenomic differences' enabled by advances in molecular genetics. Emerging technologies are poised to revolutionize the field, offering unprecedented opportunities for personalized medicine [21, 22].

- **Next-Generation Sequencing (NGS):** NGS technologies, including whole exome sequencing (WES), whole genome sequencing (WGS), and targeted sequencing, provide comprehensive genomic coverage, enabling the identification of rare and structural variants that may impact drug response. While NGS data processing is more complex, the ability to sequence entire genomes

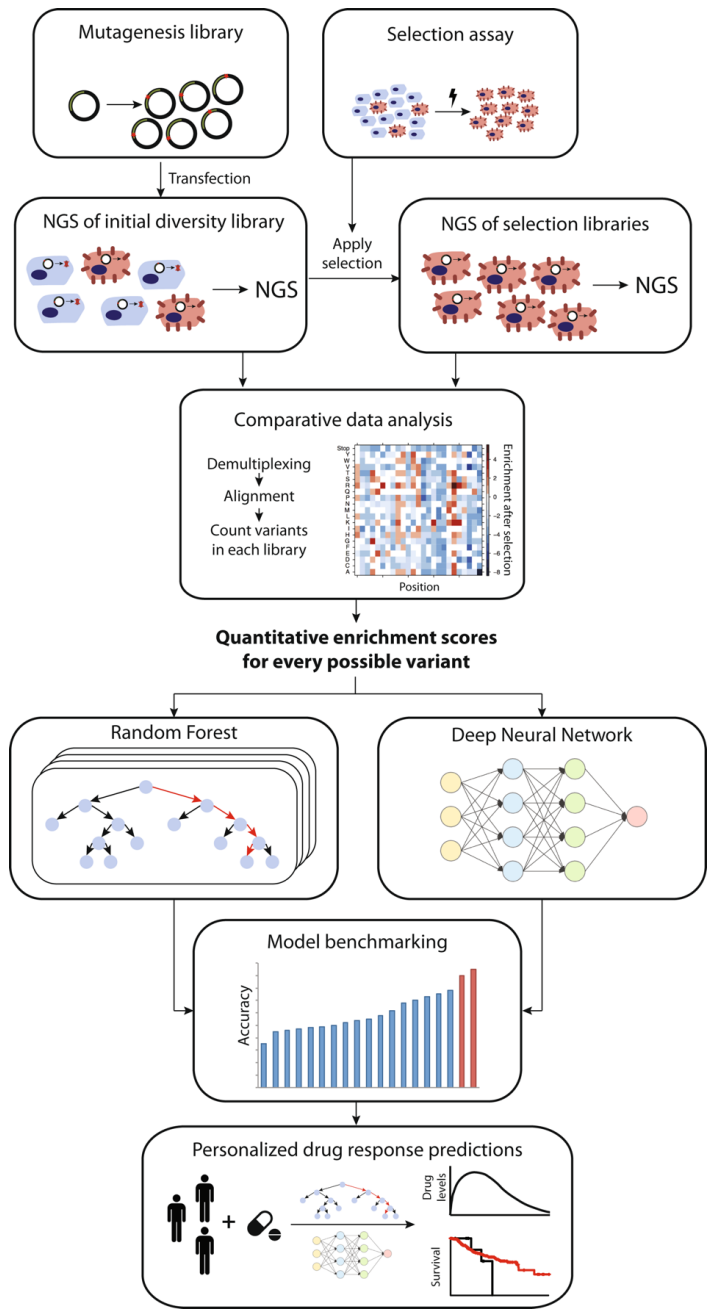


Figure 5. Amino acid substitutions

quickly and at lower cost has facilitated large-scale pharmacogenomics studies and the discovery of new drug targets.

- **Long-Read Sequencing:** Technologies like PacBio and Oxford Nanopore allow for better characterization of complex genomic regions and structural variants, which are often missed by short-read sequencing. Although currently limited to research use, long-read sequencing holds promise

for improving pharmacogenomic profiling.

- **CRISPR-Cas9 Gene Editing:** The revolutionary CRISPR-Cas9 technology enables precise genetic modifications, paving the way for developing new tools and animal models for pharmacogenomics research. This technology has the potential to accelerate the understanding of genetic variations and their impact on drug response.
- **Microfluidics:** Microfluidics technology enables studying genetic variation and drug response at the single-cell level, potentially leading to more targeted cancer treatments and personalized therapies.
- **Artificial Intelligence (AI):** AI is transforming data analysis and interpretation in pharmacogenomics, enabling precise and personalized medicine based on genetic information. Table 7 gives, AI algorithms have successfully predicted drug responses, optimized oncology treatments, and accelerated drug discovery processes.

**Table 7.** Major Technologies and their application

| Technology           | Application                                                         |
|----------------------|---------------------------------------------------------------------|
| NGS                  | Comprehensive genomic coverage, rare variant detection              |
| Long-Read Sequencing | Characterization of complex genomic regions and structural variants |
| CRISPR-Cas9          | Development of research tools and animal models                     |
| Microfluidics        | Single-cell analysis for targeted cancer treatments                 |
| AI                   | Data analysis, drug response prediction, treatment optimization     |

The integration of these cutting-edge technologies with pharmacogenomics is driving a paradigm shift towards precision medicine. As the global pharmacogenomics market is projected to grow significantly, reaching a market size of \$10.2 billion by 2025, these technological advancements will play a pivotal role in realizing the full potential of personalized medicine.

## 5. Conclusion

The field of pharmacogenomics has made significant strides in unraveling the complex interplay between genetic variation and drug response. By leveraging approaches such as genome-wide association studies, single gene variant analyses, and combinatorial pharmacogenetics, we have gained valuable insights into how genetic factors influence drug metabolism, pharmacokinetics, and pharmacodynamics. These discoveries have paved the way for personalized medicine, enabling healthcare providers to optimize drug selection, dosing, and treatment strategies based on an individual's unique genetic profile. As we continue to advance in this field, the integration of emerging technologies such as next-generation sequencing, long-read sequencing, CRISPR-Cas9 gene editing, microfluidics, and artificial intelligence will be instrumental in furthering our understanding of pharmacogenomics. Additionally, addressing challenges related to clinical implementation, regulatory frameworks, and cost-effectiveness will be crucial to realizing the full potential of personalized medicine. With ongoing research and collaboration, pharmacogenomics holds the promise of transforming healthcare, leading to improved patient outcomes and a more tailored approach to drug therapy.

## References

- [1] William E Evans and Julie A Johnson. "Pharmacogenomics: the inherited basis for interindividual differences in drug response". In: *Annual review of genomics and human genetics* 2.1 (2001), pp. 9–39.
- [2] Magnus Ingelman-Sundberg, Souren Mkrтчian, Yitian Zhou, and Volker M Lauschke. "Integrating rare genetic variants into pharmacogenetic drug response predictions". In: *Human genomics* 12 (2018), pp. 1–12.
- [3] Hans-Georg Eichler, Eric Abadie, Alasdair Breckenridge, Bruno Flamion, Lars L Gustafsson, Hubert Leufkens, Malcolm Rowland, Christian K Schneider, and Brigitte Bloechl-Daum. "Bridging the efficacy–effectiveness gap: a regulator’s perspective on addressing variability of drug response". In: *Nature reviews Drug discovery* 10.7 (2011), pp. 495–506.
- [4] TP Aneesh, Sonal Sekhar, Asha Jose, Lekshmi Chandran, and Subin Mary Zachariah. "Pharmacogenomics: the right drug to the right person". In: *Journal of clinical medicine research* 1.4 (2009), p. 191.
- [5] Volker M Lauschke, Yitian Zhou, and Magnus Ingelman-Sundberg. "Novel genetic and epigenetic factors of importance for inter-individual differences in drug disposition, response and toxicity". In: *Pharmacology & therapeutics* 197 (2019), pp. 122–152.
- [6] Kathleen M Giacomini, Claire M Brett, Russ B Altman, NL Benowitz, ME Dolan, DA Flockhart, JA Johnson, DF Hayes, T Klein, RM Krauss, et al. "The pharmacogenetics research network: from SNP discovery to clinical drug response". In: *Clinical Pharmacology & Therapeutics* 81.3 (2007), pp. 328–345.
- [7] Michel Eichelbaum, Magnus Ingelman-Sundberg, and William E Evans. "Pharmacogenomics and individualized drug therapy". In: *Annu. Rev. Med.* 57 (2006), pp. 119–137.
- [8] Heather E Wheeler, Michael L Maitland, M Eileen Dolan, Nancy J Cox, and Mark J Ratain. "Cancer pharmacogenomics: strategies and challenges". In: *Nature Reviews Genetics* 14.1 (2013), pp. 23–34.
- [9] Mikael Kozyra, Magnus Ingelman-Sundberg, and Volker M Lauschke. "Rare genetic variants in cellular transporters, metabolic enzymes, and nuclear receptors can be important determinants of interindividual differences in drug response". In: *Genetics in Medicine* 19.1 (2017), pp. 20–29.
- [10] Shabbir Ahmed, Zhan Zhou, Jie Zhou, and Shu-Qing Chen. "Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine". In: *Genomics, proteomics and bioinformatics* 14.5 (2016), pp. 298–313.
- [11] Wolfgang Sadee and Zunyan Dai. "Pharmacogenetics/genomics and personalized medicine". In: *Human molecular genetics* 14.suppl\_2 (2005), R207–R214.
- [12] Munir Pirmohamed. "Personalized pharmacogenomics: predicting efficacy and adverse drug reactions". In: *Annual review of genomics and human genetics* 15 (2014), pp. 349–370.
- [13] Giovanni Severino and Maria Del Zompo. "Adverse drug reactions: role of pharmacogenomics". In: *Pharmacological Research* 49.4 (2004), pp. 363–373.
- [14] Richard M Turner, B Kevin Park, and Munir Pirmohamed. "Parsing interindividual drug variability: an emerging role for systems pharmacology". In: *Wiley Interdisciplinary Reviews: Systems Biology and Medicine* 7.4 (2015), pp. 221–241.
- [15] Dan M Roden, Russell A Wilke, Heyo K Kroemer, and C Michael Stein. "Pharmacogenomics: the genetics of variable drug responses". In: *Circulation* 123.15 (2011), pp. 1661–1670.
- [16] BS Shastri. "Pharmacogenetics and the concept of individualized medicine". In: *The pharmacogenomics journal* 6.1 (2006), pp. 16–21.
- [17] Dan M Roden, Russ B Altman, Neal L Benowitz, David A Flockhart, Kathleen M Giacomini, Julie A Johnson, Ronald M Krauss, Howard L McLeod, Mark J Ratain, Mary V Relling, et

- al. "Pharmacogenomics: challenges and opportunities". In: *Annals of internal medicine* 145.10 (2006), pp. 749–757.
- [18] Qiang Ma and Anthony YH Lu. "Pharmacogenetics, pharmacogenomics, and individualized medicine". In: *Pharmacological reviews* 63.2 (2011), pp. 437–459.
- [19] Geoffrey T Tucker. "Advances in understanding drug metabolism and its contribution to variability in patient response". In: *Therapeutic drug monitoring* 22.1 (2000), pp. 110–113.
- [20] Ashraf G Madian, Heather E Wheeler, Richard Baker Jones, and M Eileen Dolan. "Relating human genetic variation to variation in drug responses". In: *Trends in genetics* 28.10 (2012), pp. 487–495.
- [21] Rashmi R Shah. "Pharmacogenetics in drug regulation: promise, potential and pitfalls". In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 360.1460 (2005), pp. 1617–1638.
- [22] Urs A Meyer, Ulrich M Zanger, and Matthias Schwab. "Omics and drug response". In: *Annual review of pharmacology and toxicology* 53 (2013), pp. 475–502.