EJPMR, 2026, 13(5), 11-15 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

PHARMACOGENOMICS: BRIDGING THE GAP BETWEEN GENETICS AND DRUG THERAPY

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DOI: https://doi.org/10.5281/zenodo.19882647

How to cite this Article: [1*]P. Reddy Sekhar, [1]V. Sukanya, [1]M. Guru Yatheesha, [2]Dr. C. Mohana Priya (2026). Pharmacogenomics: Bridging The Gap Between Genetics And Drug Therapy. European Journal of Pharmaceutical and Medical Research, 13(5), 11–15.

Article Received on 31/03/2026 **Article Revised on 20/04/2026** **Article Published on 01/05/2026**

ABSTRACT

Pharmacogenomics, the integration of pharmacology and genomics, lies at the center of precision medicine by personalizing drug therapy based on genetics. 20–95% of drug response variability arises due to genetic variation, which influences drug metabolism, transport, target, and immune reactions. Adverse drug reactions (ADRs), a leading cause of hospitalization and death, make personalized prescribing critical. There are a number of major pharmacogenomic applications, including cardiology dosing of warfarin and clopidogrel, cancer treatment targeted to a specific cancer, psychiatric medication optimization, and prevention of hypersensitivity to drugs like abacavir and carbamazepine. CPIC and DPWG recommendations aid clinical application, with issues of test availability, provider education, ethical issues, and patient heterogeneity persisting. Pharmacogenomic testing may be costly initially but is cost-effective by avoiding hospitalization and maximizing treatment. Technological advances in AI, CRISPR, and whole-genome sequencing hold the potential for greater incorporation into medicine. Pharmacogenomics is a new model for therapeutics that allows for safer, more efficient, and individualized medicine, with global efforts in place to provide equitable access.

KEYWORDS: Pharmacogenomics, Precision medicine, Adverse drug reactions (ADRs), Genetic polymorphisms, Personalized therapy, Whole-genome sequencing, Cost-effectiveness.

INTRODUCTION

Pharmacogenomics, the union of pharmacology and genomics, is one of the cornerstones of precision medicine, with a mission of tailoring drug therapy according to a patient's genetic makeup. Drug response heterogeneity has long been recognized in clinical practice: two patients with the same demographics and diagnosis can respond wildly differently to a particular drug. While environmental factors such as diet, comorbidities, and concomitant drug treatment are also involved, genetic heterogeneity accounts for 20–95% of drug disposition and response variability, depending on the drug.[1,2]

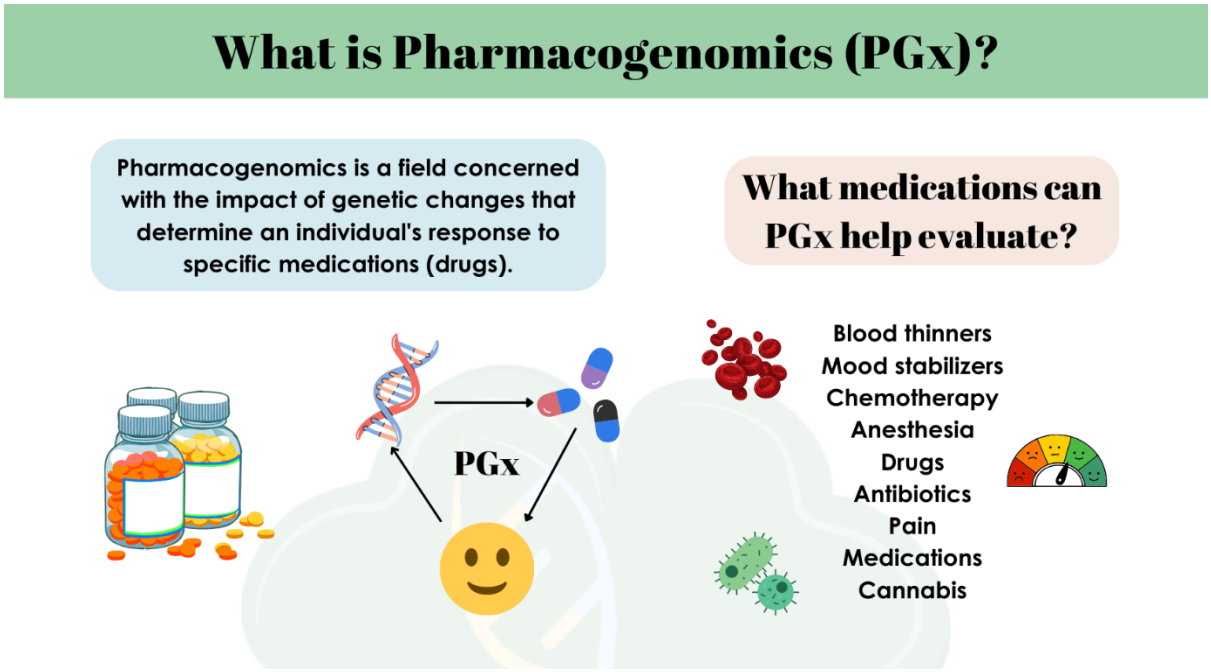

Figure 1.1: Pharmacogenomics.

Personalized medicine is necessitated by adverse drug reactions. These are associated with deaths running into over 100,000 annually in the United States alone. This translates into a leading cause of death among the top 10 most leading causes of mortality.[3] In addition, 5-10% of those admitted to hospitals are due to ADRs, adding 2-5 days to patient stays in hospitals—a cost implications—are costly.[4] Such staggering figures explain the need for a revolution in the administration of drug therapy away from a one-size-fits-all approach toward genetically targeted drug therapy.

HISTORICAL BACKGROUND OF PHARMACOGENOMICS

Drug response genetics first became apparent in the 1950s when clinicians observed idiosyncratic responses to primaquine by patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[5] Genetic difference in butyrylcholinesterase explained prolonged paralysis after succinylcholine treatment in anaesthesia.[6] These initial observations marked the foundation for modern-day pharmacogenomics.

The success of the Human Genome Project in 2003 marked a beginning of a new era of research, in which single-nucleotide polymorphisms are recognized in the genome. A total of more than 20,000 genetic variations with potential pharmacological relevance are found, and hundreds have been linked with drug response in the context of the clinic setting.[7]

NEED OF PHARMACOGENOMICS

The rationale for pharmacogenomics is based on the large variability of drug response among individuals. Genetic contributions range from 20% to 95% variability for drug disposition and response depending on the drug in question.[1,2] Patients often present with either sub-therapeutic or toxic responses to standardized drug administration schedules owing to genetic differences in drug metabolizing enzymes, transporters, and receptors.

Adverse drug reactions (ADRs) are a significant burden on the global healthcare system and rank among the top causes of hospitalization and death.[3,4] Moreover, the past decade has witnessed the rapid discovery of gene-drug associations with clinical relevance owing to the Human Genome Project.[7] Therefore, pharmacogenomics is not a new field but a pressing need for enhanced patient safety, therapeutic efficacy, and cost-effective healthcare.

MECHANISMS OF GENETIC INFLUENCE ON DRUG RESPONSE

Genetic variability influences drug response primarily through

1. **Drug-Metabolizing Enzymes** – Polymorphisms in genes of the cytochrome P450 (CYP450) gene family (e.g., CYP2D6, CYP2C19, CYP2C9) determine the metabolism of almost 75% of drugs that are administered therapeutically.[8] Patients can be poor, intermediate, extensive, or ultra-rapid metabolizers based upon genetic variants.
2. **Drug Transporters** – Variants of ABCB1 (P-glycoprotein) regulate the pharmacokinetics of digoxin, tacrolimus, and antiretrovirals.[9]
3. **Drug Targets** – There might be modifications in the compound DNA that encodes drug receptors or targets. For instance, VKORC1 variants reduce warfarin sensitivity.[10]
4. **Immune System Genes** - The HLA region has also been linked to severe hypersensitivity reactions as seen with the abacavir-HLA B5701 or carbamazepine-HLA B1502 associations.[11]

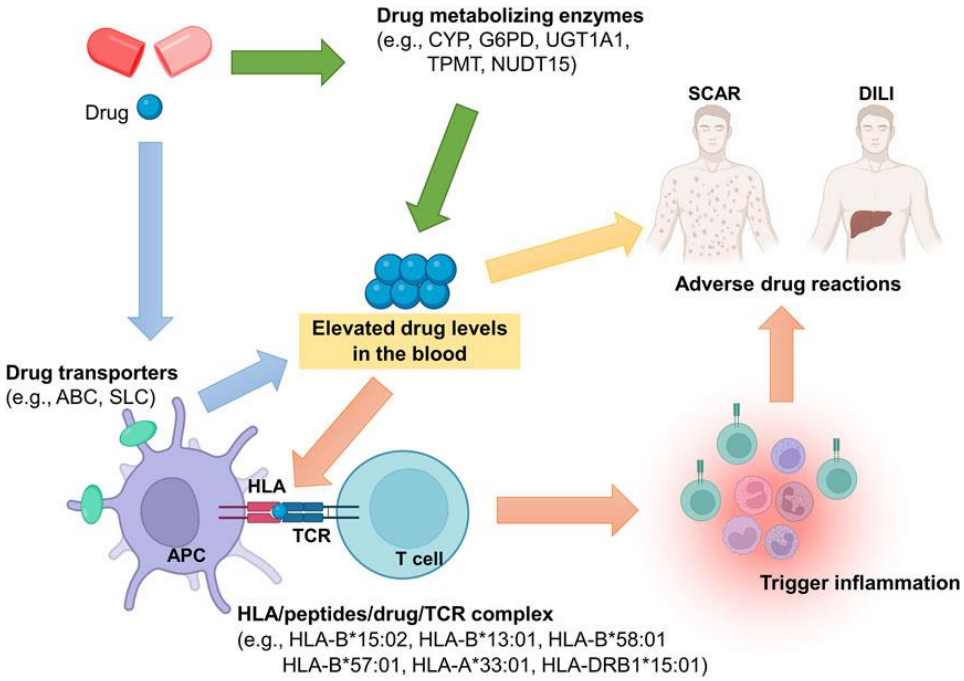

Figure 1.2: Mechanisms Of Genetic Influence on Drug Response.

CLINICAL USES OF PHARMACOGENOMICS

1. Cardiology

- Warfarin dosing is hugely influenced by CYP2C9 and VKORC1 polymorphisms. Genetic testing reduces the risk of over-anticoagulation, bleeding, and thromboembolic events.[12]
- Clopidogrel response is affected by CYP2C19 variants. Loss-of-function alleles are at higher risk of stent thrombosis and thus alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) is preferable.[13]

2. Oncology

- Thiopurines (azathioprine, 6-mercaptopurine): TPMT and NUDT15 polymorphisms predict severe myelosuppression; screening is now routine before therapy.[14]
- Irinotecan: Homozygous individuals for UGT1A1*28 have a 3–4-fold elevated risk of neutropenia and diarrhoea.[15]
- Treatment selection in lung cancer based on EGFR mutations and ALK rearrangements has revolutionized so that only those patients who are responsive receive the targeted therapies.[16]

3. Psychiatry

- Allelic variants of CYP2D6 and CYP2C19 impact plasma concentrations of antidepressants such as SSRIs and tricyclics, and antipsychotics. Genetic adjustment of Prescription reduces side effects and improve therapeutic outcomes.[17]

4. Infectious Diseases

- HLA-B*5701 screening has nearly eliminated abacavir hypersensitivity, which was previously seen in 5–8% of patients.[18]
- IL28B (IFNL3) polymorphisms were applied to predict response to interferon-based treatment of hepatitis C, though now replaced by direct-acting antivirals.[19]

5. Global Implementation and Clinical Guidelines

DPWG and CPIC provide consistent guidelines for more than 60 gene–drug pairs.[20] For example.

- CYP2C19–Clopidogrel: Alternative drugs must be prescribed in poor metabolizers.
- TPMT/NUDT15–Thiopurines: Dosage adjustment or alternative therapy should be proposed.
- HLA-B*1502–Carbamazepine: Avoid in carriers (common in Asian populations).

Other countries such as the United States, Netherlands, Japan, and Singapore have begun integrating pharmacogenomic testing into regular healthcare. Adoption remains low in low- and middle-income countries due to infrastructural and cost barriers.[21]

ECONOMIC AND HEALTHCARE IMPACT

Pharmacogenomic testing generates long-term savings although at some initial costs. For instance.

- Genotyping of warfarin reduces hospitalization for bleeding and thromboembolism at a saving of approximately ₹1,36,430.63 per patient annually.[22]
- Pre-emptive multi-gene panel testing was estimated to be ₹36,38,334.95 per QALY gained and is within cost-effectiveness levels.[23]
- Prevention of abacavir hypersensitivity by HLA-B*5701 screening not only saves lives but also reduces hospitalization expense for serious adverse effects.[24]

BARRIERS TO IMPLEMENTATION

1. Accessibility of testing – While sequencing fees have fallen from ₹9,09,595.00 in 2011 to under ₹90,959.50 today, turnaround and availability of certified laboratories are still obstacles.[25]
2. Clinician Knowledge Gap – Less than 25–35% of physicians are self-assured in interpreting pharmacogenomic tests.[26]
3. Ethical, Legal, and Social Issues (ELSI) – Genetic privacy, insurance discrimination, and ownership of data concerns are barriers.[27]
4. Population Diversity – European ancestry population data predominate most available data; limited data in African, Asian, and Indigenous populations risk exacerbating disparities.[28]

FUTURE PERSPECTIVES

Pharmacogenomics is moving from single-gene testing to panel-based and whole-genome approaches. Key trends are.

- **Integration with Electronic Health Records (EHRs):** Computerized alerts for gene–drug interactions during prescribing.[29]
- **Artificial Intelligence (AI):** The integration of different genome, epigenome, microbiome, and environment data using machine learning algorithms for precise prediction.[30]
- **CRISPR and Gene Therapy:** Capability to edit pathogenic variants limiting drug metabolism.[31]
- **International Initiatives:** Programs such as the All of Us Research Program aim to increase diversity within gene pools to ensure that pharmacogenomics has equal benefit for all.[32]

PROCESS OF PHARMACOGENOMICS

1. Identification of Candidate Genes

Candidate genes involved with pharmaceutical dynamics and kinetics like drug targets, transporters, and CYP450 enzymes are known because of existing gene-drug interaction databases.[8,10]

2. Genetic Testing and Genotyping

Patient sample DNA (blood or saliva) will be extracted, and polymorphisms will be identified through genotyping or sequencing—even when the cost of sequencing is lower than before.[25]

3. Genotype-to-Phenotype Translation

Genetic variants can be converted to metabolizer phenotype (poor, intermediate, normal, or ultra-rapid metabolizers)—which can be applied to drug dosage.[8]

4. Clinical Interpretation Using Guidelines

Organizations such as CPIC and DPWG have established clinical guidelines for clinicians to utilize genetic information for clinical practice through published evidence-based recommendations.[20,29]

5. Integration into Clinical Workflow

Pharmacogenomic data will be incorporated into electronic health records and be linked to alerts for real-time clinical decision-making.[29]

DISCUSSION

Pharmacogenomics is an innovative concept in precision medicine, and this concept shows promise in terms of its utility in tailoring their therapies according to their genetic background. The relevance in the field can be understood in terms of the avoidance of ADRs, reduction in hospitalization, and optimization of therapeutic effect. The concept can be best utilized in cardiology, oncology, psychiatry, and in the field of infectiology. From the concept of single-gene tests, nowadays multiple gene tests are a part, and sequencing of the entire genome can be done to make its utility more predictable. Even though the concept has potential in terms of its utility in the future, its non-availability and its expensive nature, along with a lack of skilled personnel in healthcare facilities, make it impossible for its widespread use. Additionally, in most cases, this information relates to the European population; therefore, its utility in a diverse population cannot be guaranteed. International effort will be the key driver to level the benefits, enabling pharmacogenomics to be a mainstay in future personalized medicine.

CONCLUSION

Pharmacogenomics revolutionized the science of drug therapy with clinicians because it closes the gap between pharmacology and genetics well. In this way, it does make drug therapy safer, more effective, and less costly by identifying variations in how genetics affect drug use. Despite hurdles with accessibility, education, and equality of implementation, pharmacogenomics must be used in practice because of its profound potential to alter lives. Therefore, with the advancement of genomics, AI, and data-sharing tools across the world, pharmacogenomics will certainly shape the future of therapeutics.

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