

Role of Pharmacogenomics in Personalized Drug Therapy: Current Evidence, Clinical Applications, and Future Perspectives

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ABSTRACT

Pharmacogenomics has emerged as a cornerstone of precision medicine by providing insights into how inherited genetic variations influence individual responses to drug therapy. Genetic polymorphisms affecting drug-metabolizing enzymes, transporters, receptors, and signalling pathways contribute significantly to interindividual variability in drug efficacy, toxicity, and therapeutic outcomes. Over the past two decades, advances in molecular genetics, high-throughput sequencing technologies, and bioinformatics have accelerated the translation of pharmacogenomic discoveries into clinical practice, enabling genotype-guided prescribing across multiple therapeutic areas, including oncology, cardiovascular diseases, psychiatry, infectious diseases, transplantation, and pain management. This review comprehensively examines the molecular basis of pharmacogenomics, major pharmacogenes involved in drug response, clinically actionable gene-drug interactions, current international guidelines, pharmacogenomic testing technologies, and the growing role of artificial intelligence and digital health in precision therapeutics. The review also discusses the challenges limiting widespread clinical implementation, including limited population-specific evidence, economic and infrastructural constraints, ethical and legal considerations, inadequate clinician awareness, and the need for standardized testing and reporting. Particular emphasis is placed on the current status of pharmacogenomics in India, highlighting national genomic initiatives, implementation challenges, and future opportunities in a genetically diverse population. Emerging advances in multi-omics integration, whole-genome sequencing, clinical decision-support systems, and predictive analytics are expected to further strengthen the clinical utility of pharmacogenomics and facilitate its integration into routine healthcare. As scientific evidence and implementation strategies continue to evolve, pharmacogenomics has the potential to optimize drug selection, individualize dosing, minimize adverse drug reactions, improve therapeutic outcomes, and advance the global transition toward safer, more effective, and patient-centered personalized medicine.

Keywords: Genotype-guided therapy, Personalized Medicine, Pharmacogenetic Testing, Pharmacogenomics, Precision Medicine.

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INTRODUCTION

The remarkable progress achieved in pharmacotherapy over the past century has transformed the management of acute and chronic diseases, substantially improving patient survival, quality of life, and healthcare outcomes. Despite these advances, considerable interindividual variability in drug response remains an important challenge in clinical medicine. Patients receiving the same medication at similar doses may experience markedly

different outcomes, ranging from optimal therapeutic benefit to treatment failure or serious Adverse Drug Reactions (ADRs). Such variability reflects the complex interaction of genetic, physiological, environmental, pathological, and lifestyle factors that influence drug disposition and pharmacological response (Pirmohamed, 2023; Motulsky, 1957; Kalow, 2006; Evans and McLeod, 2003; Lauschke and Ingelman-Sundberg, 2026). The recognition that inherited genetic variation contributes substantially to this variability has fundamentally changed the understanding of drug therapy and established an important scientific basis for pharmacogenomics and precision medicine (Pirmohamed, 2023; Evans and McLeod, 2003; Lauschke and Ingelman-Sundberg, 2026).

The limitations of the traditional “one-size-fits-all” approach have become increasingly apparent with the growing complexity of



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modern pharmacotherapy. Conventional prescribing strategies are largely based on population averages and assume that patients with similar clinical characteristics will respond comparably to the same therapeutic regimen. In reality, substantial differences occur in drug absorption, distribution, metabolism, excretion, and pharmacodynamic response. Clinical factors such as age, sex, body composition, hepatic and renal function, comorbidities, concomitant medications, nutritional status, and environmental exposures contribute to this variability. In addition, inherited polymorphisms affecting drug-metabolizing enzymes, membrane transporters, receptors, signalling proteins, and immune-response pathways can substantially modify drug efficacy and toxicity (Pirmohamed, 2023; Evans and McLeod, 2003; Relling and Evans, 2015).

The clinical consequences of variability in drug response are particularly evident in the burden of ADRs. ADRs contribute substantially to morbidity, mortality, healthcare utilization, and treatment costs. Importantly, some serious ADRs are predictable and potentially preventable because they arise from inherited differences in drug metabolism or immune-mediated drug responses. Identification of clinically actionable pharmacogenomic variants therefore provides an opportunity to predict susceptibility to selected toxicities before treatment initiation and to guide drug selection or dose optimization (Pirmohamed, 2023; Phillips *et al.*, 2001).

The conceptual origins of pharmacogenomics can be traced to the pioneering work of Arno Motulsky, who proposed in 1957 that inherited biochemical differences could explain individual variation in drug response. Werner Kalow subsequently contributed substantially to the understanding of inherited variation in drug metabolism, while Friedrich Vogel introduced the term *pharmacogenetics* in 1959. These landmark observations established the scientific foundation for investigating inherited variability in pharmacotherapy (Motulsky, 1957; Kalow, 2006; Vogel, 1959; Lander *et al.*, 2001; Venter *et al.*, 2001; Kalow, 2004). The completion of the Human Genome Project in 2001, together with advances in high-throughput genotyping, Genome-Wide Association Studies (GWAS), and next-generation sequencing, subsequently transformed the field from the study of individual genetic effects into the broader genome-wide discipline of pharmacogenomics (Lander *et al.*, 2001; Venter *et al.*, 2001; Kalow, 2004).

Fundamentals of Pharmacogenomics

Pharmacogenomics is the study of how genetic variation influences individual responses to medications. It integrates pharmacology, molecular genetics, genomics, bioinformatics, and clinical medicine to identify genetic determinants of drug efficacy, toxicity, and dosage requirements. Pharmacogenetics traditionally focused on individual genes or variants, whereas pharmacogenomics adopts a broader genome-wide perspective

and considers interactions among multiple genetic and clinical determinants of drug response (Pirmohamed, 2023; Evans and McLeod, 2003; Relling and Evans, 2015; Caudle *et al.*, 2017).

The transition from pharmacogenetics to pharmacogenomics has been facilitated by major advances in genomic technologies, including high-throughput genotyping, GWAS, Next-Generation Sequencing (NGS), Whole-Exome Sequencing (WES), and Whole-Genome Sequencing (WGS). These technologies have enabled identification of genetic variants associated with drug metabolism, transport, therapeutic targets, immune-mediated drug reactions, and treatment response. Integration of genomic information with resources such as Pharm GKB has further facilitated translation of genetic discoveries into clinically actionable recommendations (Thorn *et al.*, 2013; Roden *et al.*, 2011).

Drug response is a complex phenotype resulting from interactions among genetic, environmental, physiological, and disease-related factors. Pharmacokinetics describes drug absorption, distribution, metabolism, and excretion, whereas pharmacodynamics describes the interaction of a drug with its biological targets and the resulting therapeutic or toxic effects. Genetic variation can influence either or both pathways, producing substantial interindividual differences in drug exposure and clinical response (Evans and McLeod, 2003; Caudle *et al.*, 2017; Ingelman-Sundberg, 2004).

Pharmacokinetic Variability

Pharmacokinetic variability is strongly influenced by polymorphisms in genes encoding drug-metabolizing enzymes and membrane transport proteins. Cytochrome P450 (CYP450) enzymes metabolize a large proportion of clinically used medications. Variants in genes such as *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A5*, and *CYP2B6* can alter enzyme activity and produce distinct metabolizer phenotypes. Reduced enzyme activity may increase systemic drug exposure and toxicity, whereas increased activity may reduce exposure and therapeutic efficacy (Ingelman-Sundberg, 2004; Meyer, 2000; Wilkinson, 2005).

Phase II metabolic pathways also contribute substantially to pharmacokinetic variability. Genetic variation in *TPMT* and *NUDT15* can markedly alter thiopurine metabolism and increase the risk of severe myelosuppression. Similarly, reduced activity of *DPYD*, which encodes dihydropyrimidine dehydrogenase, increases exposure to fluoropyrimidines and predisposes susceptible patients to severe and potentially life-threatening toxicity (Relling *et al.*, 2019; Amstutz *et al.*, 2018).

Drug transport proteins provide another important source of pharmacokinetic variability. ATP-binding cassette and solute carrier transporters regulate drug absorption, distribution, hepatic uptake, and elimination. A well-established example is

SLCO1B1, which encodes the hepatic transporter OATP1B1. The *SLCO1B1* c.521T>C variant reduces hepatic uptake of simvastatin and increases systemic exposure and the risk of statin-associated myopathy (Niemi *et al.*, 2011; Link *et al.*, 2008).

Pharmacodynamic Variability

Pharmacodynamic genes influence drug effects by altering receptors, enzymes, ion channels, signaling pathways, or immune recognition. Consequently, individuals with comparable plasma drug concentrations may experience different therapeutic or toxic responses because of genetic differences in drug targets (Evans and McLeod, 2003; Caudle *et al.*, 2017).

Clinically relevant examples include *VKORC1*, which contributes to warfarin dose variability, and somatic biomarkers such as *EGFR*, *KRAS*, and *BRAF*, which influence selection of targeted anticancer therapies. HLA variation also has major clinical importance because particular HLA alleles predispose genetically susceptible individuals to severe immune-mediated drug reactions (Relling and Klein, 2011; Whirl-Carrillo *et al.*, 2021; Roden *et al.*, 2019).

Genetic Polymorphisms and Functional Consequences

Genetic variation occurs in multiple forms, including single nucleotide variants, insertions, deletions, Copy Number Variations (CNVs), tandem repeats, and structural variants. Depending on their location and functional effect, variants may alter amino acid sequence, gene expression, messenger RNA splicing, protein stability, or enzyme activity (Thorn *et al.*, 2013; Lauschke *et al.*, 2024).

The clinical significance of a pharmacogenomic variant also depends on its population frequency. Important pharmacogenetic alleles are not distributed uniformly across populations. For example, *CYP2C19* loss-of-function alleles are more frequent in several East Asian populations, while *NUDT15* variants associated with thiopurine intolerance are particularly important in Asian populations. Population diversity therefore needs to be considered when interpreting pharmacogenomic findings and designing equitable precision-medicine strategies (Table 1) (Bush and Moore, 2012; Lauschke *et al.*, 2022; Zhou *et al.*, 2025).

Genetic Variability Influencing Drug Response

Interindividual variability in drug response is driven by inherited genetic differences that influence pharmacokinetic and pharmacodynamic processes. Environmental factors, disease states, age, sex, diet, and concomitant medications also contribute; however, genetic variation is an important determinant of differences in drug efficacy, toxicity, and dosage requirements (Pirmohamed, 2023; Evans and McLeod, 2003; Relling and Evans, 2015; Roden *et al.*, 2011).

Single nucleotide variants represent one of the most common forms of genetic variation relevant to pharmacogenomics. They may influence protein structure, enzyme activity, transcriptional regulation, or messenger RNA stability. Many variants are clinically neutral, whereas others have sufficiently reproducible effects to be incorporated into pharmacogenomic guidelines (Caudle *et al.*, 2017; Lauschke *et al.*, 2024).

Structural variation is also important. CNVs are particularly relevant to *CYP2D6*, where gene deletion may result in absent enzyme activity and gene duplication or multiplication may contribute to ultrarapid metabolism. Accurate characterization of *CYP2D6* can therefore require methods capable of detecting both sequence variation and copy-number changes.

Genetic variants influence drug response principally through pharmacokinetic and pharmacodynamic mechanisms. Pharmacokinetic variability changes systemic drug concentrations through effects on ADME processes, while pharmacodynamic variability alters target sensitivity, signalling, enzyme activity, or immune recognition (Evans and McLeod, 2003; Ingelman-Sundberg, 2004; Wilkinson, 2005).

The CYP450 family remains one of the most clinically important groups of pharmacogenes. Functional polymorphisms in *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A5*, and *CYP2B6* produce distinct metabolizer phenotypes and have implications for several therapeutic classes, including antidepressants, opioids, antiplatelet agents, immunosuppressants, and anticoagulants (Ingelman-Sundberg, 2004; Meyer, 2000; Wilkinson, 2005; Relling and Klein, 2011).

Drug transporters also influence pharmacokinetic variability. Variants in *SLCO1B1*, *ABCB1*, and other transporter genes can alter drug disposition. The *SLCO1B1* c.521T>C variant is a well-characterized example because reduced transporter activity increases simvastatin exposure and myopathy risk (Niemi *et al.*, 2011; Link *et al.*, 2008). Pharmacodynamic variability is particularly important for immune-mediated adverse reactions. HLA-B*57:01 is strongly associated with abacavir hypersensitivity, HLA-B*15:02 with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in susceptible populations, and HLA-B*58:01 with severe cutaneous adverse reactions to allopurinol (Mallal *et al.*, 2002; Mallal *et al.*, 2008; Chung *et al.*, 2004; Saito *et al.*, 2016).

Population-specific differences in pharmacogenomic variation are clinically important. Differences in allele frequencies and linkage patterns can affect the applicability of findings generated in one population to another. This emphasizes the need for genomic research that adequately represents diverse populations (Bush and Moore, 2012; Lauschke *et al.*, 2022; Zhou *et al.*, 2025). Overall, genetic variability provides the biological rationale for genotype-guided prescribing and supports the transition from

Table 1: Types of genetic variation influencing drug response.

Type of variation	Description	Example gene	Clinical significance
Single nucleotide variant	Single-base substitution	CYP2C19	Altered enzyme activity
Copy number variation	Gene deletion or duplication	CYP2D6	Poor or ultrarapid metabolism
Insertion/deletion	Addition or loss of DNA bases	DPYD	Increased fluoropyrimidine toxicity
Tandem repeat	Repeated DNA sequence	UGT1A1	Altered glucuronidation
HLA polymorphism	Immune-related genetic variation	HLA-B*57:01	Drug hypersensitivity

empirical treatment toward individualized pharmacotherapy (Table 2).

Major Pharmacogenes and their Clinical Significance

The successful implementation of pharmacogenomics depends on identification of pharmacogenes with reproducible and clinically actionable gene-drug associations. CPIC and DPWG have translated evidence for selected gene-drug pairs into prescribing recommendations, enabling clinicians to incorporate genotype information into therapeutic decision-making (Caudle *et al.*, 2021; Swen *et al.*, 2023).

Cytochrome P450 Enzyme Family

CYP450 enzymes constitute the most extensively studied group of pharmacogenes. Functional polymorphisms alter enzyme activity and produce predictable metabolizer phenotypes. *CYP2D6* is involved in the metabolism of numerous antidepressants, antipsychotics, β -blockers, opioids, and other drugs. Structural variation and multiple star alleles contribute to substantial interindividual variability. *CYP2D6* activity-score approaches help translate genotype information into clinically meaningful metabolizer phenotypes (Gaedigk *et al.*, 2019; Gaedigk *et al.*, 2008; Meyer, 2004).

CYP2C19 is particularly important in cardiovascular medicine because reduced-function alleles impair activation of clopidogrel and may increase the risk of adverse cardiovascular outcomes in susceptible patients (Pereira *et al.*, 2020; Lee *et al.*, 2022). CYP2C9 contributes to variability in warfarin and phenytoin metabolism, while CYP3A5 is particularly relevant to tacrolimus therapy in transplantation (Ingelman-Sundberg, 2004; Relling and Klein, 2011).

Phase II Drug-Metabolizing Enzymes

TPMT and *NUDT15* are important determinants of thiopurine toxicity. Reduced activity increases the risk of severe myelosuppression, and genotype-guided dose reduction or alternative therapy can improve safety. *DPYD* encodes the rate-limiting enzyme involved in fluoropyrimidine catabolism. Reduced *DPYD* activity increases exposure to fluorouracil and capecitabine and can result in severe gastrointestinal, hematological, neurological, and mucocutaneous toxicity. Pre-treatment *DPYD* testing is therefore clinically important

when fluoropyrimidine therapy is being considered (Amstutz *et al.*, 2018; Henricks *et al.*, 2018). *UGT1A1* variation can influence irinotecan toxicity and may assist in identifying patients at increased risk of severe neutropenia (Innocenti *et al.*, 2014).

Drug Transporter Genes

SLCO1B1 encodes OATP1B1 and is an established determinant of statin disposition. Reduced-function variants increase circulating statin concentrations and myopathy risk (Niemi *et al.*, 2011; Link *et al.*, 2008). Other transporters, including *ABCB1*, *ABCG2*, and *SLC22A1*, have been investigated in relation to numerous medications. However, evidence for routine clinical implementation is less consistent for many transporter gene-drug pairs than for established CYP, *DPYD*, *TPMT*, *NUDT15*, and HLA associations.

Human Leukocyte Antigen Genes

HLA variants influence immune-mediated drug reactions. HLA-B*57:01 screening before abacavir therapy is a well-established example of pharmacogenomic testing preventing severe hypersensitivity (Mallal *et al.*, 2002; Mallal *et al.*, 2008). HLA-B*15:02 testing before carbamazepine therapy is recommended for genetically susceptible populations because of the strong association with SJS/TEN (Chung *et al.*, 2004). HLA-B*58:01 is associated with allopurinol-induced severe cutaneous adverse reactions and represents another important example of genotype-guided prevention of serious ADRs (Saito *et al.*, 2016).

Emerging Pharmacogenes

Additional clinically relevant pharmacogenes include *RYR1* and *CACNA1S* for malignant hyperthermia susceptibility and *G6PD* for susceptibility to hemolysis with selected oxidant drugs. Continued functional characterization of rare and structural variants is expected to expand the number of clinically actionable pharmacogenomic biomarkers (Lauschke *et al.*, 2024; Ingelman-Sundberg *et al.*, 2018).

Clinical Applications of Pharmacogenomics

Translation of pharmacogenomic discoveries into clinical practice enables individualized drug selection and dosing and may reduce preventable toxicity. The strongest clinical evidence currently exists for selected gene-drug pairs in cardiovascular

medicine, oncology, infectious diseases, psychiatry, neurology, and transplantation (Caudle *et al.*, 2021; Phillips *et al.*, 2018).

Cardiovascular Medicine

Clopidogrel is one of the best-established cardiovascular applications. Because it is a prodrug requiring CYP2C19-mediated bioactivation, reduced-function CYP2C19 alleles can result in reduced active-metabolite formation and diminished platelet inhibition. Genotype-guided selection of alternative P2Y₁₂ inhibitors has been investigated in prospective clinical trials, including TAILOR-PCI (Pereira *et al.*, 2020; Lee *et al.*, 2022).

Warfarin dosing is also influenced by CYP2C9 and VKORC1 variation. Incorporation of genetic information into dosing algorithms can improve prediction of dose requirements, although clinical implementation must consider patient-specific factors and available alternatives.

Oncology

DPYD testing can identify patients at increased risk of severe fluoropyrimidine toxicity. Prospective genotype-guided dose individualization has demonstrated that pre-treatment DPYD testing can reduce severe toxicity while maintaining treatment efficacy (Amstutz *et al.*, 2018; Henricks *et al.*, 2018). UGT1A1 genotype information may also contribute to individualized irinotecan therapy, particularly in patients at increased risk of neutropenia (Innocenti *et al.*, 2014). In addition to germline pharmacogenomics, somatic biomarkers such as EGFR, ALK, KRAS, BRAF, and HER2 guide targeted cancer therapy and demonstrate the broader integration of genomic information into oncology.

Psychiatry and Neurology

CYP2D6 and CYP2C19 variants influence exposure to several antidepressants and other psychotropic medications.

Pharmacogenomic-guided prescribing has been associated with improved outcomes in selected patient populations, although the magnitude of clinical benefit varies among studies (Bousman *et al.*, 2019; Brown *et al.*, 2020). In neurology, HLA testing is particularly relevant to carbamazepine therapy in populations with a high prevalence of HLA-B*15:02 (Chung *et al.*, 2004).

Infectious Diseases

HLA-B*57:01 testing before abacavir treatment is one of the most successful examples of pharmacogenomic implementation. Prospective screening substantially reduced clinically confirmed abacavir hypersensitivity (Mallal *et al.*, 2002; Mallal *et al.*, 2008).

Transplantation Medicine

CYP3A5 genotype influences tacrolimus metabolism. CYP3A5 expressers generally require higher doses than non-expressers to achieve therapeutic concentrations. Genotype-guided initial dosing may facilitate earlier achievement of target concentrations when combined with therapeutic drug monitoring.

Future Expansion

Pharmacogenomics is expanding into additional therapeutic areas as evidence accumulates and testing becomes more accessible. Pre-emptive testing, electronic health-record integration, and clinical decision support may facilitate broader implementation (Rim *et al.*, 2025; van der Wouden *et al.*, 2017) (Table 3).

Pharmacogenomic Guidelines, Databases, and Regulatory Landscape

Successful clinical implementation requires standardized evidence-based frameworks for translating genetic findings into prescribing recommendations. CPIC, DPWG, PharmGKB, PharmVar, regulatory agencies, and clinical decision-support systems have all contributed to this process (Caudle *et al.*, 2021; Swen *et al.*, 2023; Whirl-Carrillo *et al.*, 2012; Gammal *et al.*, 2024;

Table 2: Major clinically actionable pharmacogenes and associated drugs.

Gene	Major drugs	Primary clinical consequence
CYP2D6	Codeine, tramadol, antidepressants	Altered metabolism and efficacy
CYP2C19	Clopidogrel, proton-pump inhibitors, selected antidepressants	Altered activation or clearance
CYP2C9	Warfarin, phenytoin, selected NSAIDs	Altered exposure and toxicity
CYP3A5	Tacrolimus	Individualized dose requirement
TPMT	Azathioprine, mercaptopurine	Myelosuppression
NUDT15	Thiopurines	Severe leukopenia/myelosuppression
DPYD	Fluorouracil, capecitabine	Severe fluoropyrimidine toxicity
SLCO1B1	Simvastatin	Statin-associated myopathy
HLA-B*57:01	Abacavir	Hypersensitivity
HLA-B*15:02	Carbamazepine	Stevens-Johnson syndrome/TEN
HLA-B*58:01	Allopurinol	Severe cutaneous adverse reactions

Table 3: Clinical applications of pharmacogenomics.

Specialty	Pharmacogene	Drug(s)	Clinical implication
Cardiology	CYP2C19	Clopidogrel	Alternative antiplatelet therapy in reduced-function phenotypes
Cardiology	CYP2C9, VKORC1	Warfarin	Individualized dose selection
Oncology	DPYD	Fluorouracil, capecitabine	Reduce severe toxicity
Oncology	UGT1A1	Irinotecan	Identify increased toxicity risk
Oncology	TPMT, NUDT15	Thiopurines	Prevent severe myelosuppression
Psychiatry	CYP2D6, CYP2C19	Antidepressants	Exposure-guided treatment
Infectious diseases	HLA-B*57:01	Abacavir	Prevent hypersensitivity
Neurology	HLA-B*15:02	Carbamazepine	Reduce SJS/TEN risk
Transplantation	CYP3A5	Tacrolimus	Individualized initial dosing

Koopmann *et al.*, 2022; Gaedigk *et al.*, 2018; Sangkuhl *et al.*, 2020).

Clinical Pharmacogenetics Implementation Consortium

CPIC develops evidence-based recommendations describing how available genotype information should be used to guide medication selection or dosing. Its guidelines cover numerous clinically relevant gene-drug pairs, including *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A5*, *TPMT*, *NUDT15*, *DPYD*, *SLCO1B1*, and selected HLA genes (Caudle *et al.*, 2021; Gammal *et al.*, 2024).

Dutch Pharmacogenetics Working Group

DPWG has developed pharmacogenomic guidelines that are widely used in Europe. Although CPIC and DPWG recommendations are generally concordant for many gene-drug pairs, differences can occur because of methodological and clinical considerations (Swen *et al.*, 2023; Koopmann *et al.*, 2022).

Pharmacogenomic Knowledgebases

PharmGKB provides curated information regarding gene-drug associations, clinical annotations, guidelines, and drug labels (Whirl-Carrillo *et al.*, 2012). PharmVar provides standardized pharmacogene and star-allele nomenclature, while PharmCAT assists in converting genetic findings into CPIC-based clinical annotations (Gaedigk *et al.*, 2018; Sangkuhl *et al.*, 2020).

Regulatory Agencies and Drug Labelling

Regulatory agencies increasingly incorporate pharmacogenomic information into drug labelling. Such information may identify recommendations for genetic testing, dose modification, contraindications, or altered pharmacokinetics and pharmacodynamics.

Clinical Decision Support Systems

Clinical decision-support systems integrated into electronic health records can automatically identify actionable gene-drug

interactions and provide prescribing recommendations at the point of care. Such systems can facilitate consistent use of pharmacogenomic information and reduce interpretation errors (Hicks *et al.*, 2016; Weitzel *et al.*, 2024).

Global Harmonization

International harmonization of laboratory testing, nomenclature, phenotype classification, reporting, and clinical recommendations remains important for expanding pharmacogenomic implementation (van der Wouden *et al.*, 2021) (Table 4).

Pharmacogenomic Testing Technologies

Clinical pharmacogenomics depends on accurate and reliable technologies capable of detecting relevant genetic variants. The appropriate testing method depends on the clinical question, required turnaround time, variant complexity, cost, and available laboratory infrastructure (van der Lee *et al.*, 2020; Russell *et al.*, 2021; Tafazoli *et al.*, 2021).

PCR-Based Genotyping

PCR-based methods are widely used for predefined clinically actionable variants because of their speed, analytical accuracy, and relatively low cost. Their principal limitation is that they generally detect only variants included in the assay design and may not adequately identify novel variants or complex structural variation.

Microarray Platforms

Microarrays allow simultaneous interrogation of large numbers of predefined variants and are useful for pre-emptive pharmacogenomic screening. Their major limitation is restricted detection of variants not represented on the array.

Next-Generation Sequencing

NGS enables analysis of multiple pharmacogenes and can identify both common and rare variants. It is particularly useful for pharmacogenes with extensive allelic diversity. However,

interpretation of rare variants, structural variation, and complex haplotypes requires sophisticated bioinformatics (Russell *et al.*, 2021; Tafazoli *et al.*, 2021; Enko *et al.*, 2023).

Long-Read Sequencing

Long-read sequencing can improve characterization of structural variants, copy-number changes, and complex haplotypes that may be difficult to resolve with conventional short-read methods. Its current limitations include cost, technical complexity, and limited availability.

Multi-Omics Technologies

Future pharmacogenomic testing is likely to integrate genomic information with transcriptomics, epigenomics, proteomics, metabolomics, and other molecular datasets. These approaches may improve understanding of biological mechanisms underlying variable drug response, although many remain primarily research tools (Hasin *et al.*, 2017; Karczewski and Snyder, 2018) (Table 5).

Artificial Intelligence and Digital Health in Pharmacogenomics

The expansion of genomic sequencing has generated large and complex datasets that require advanced analytical approaches.

Artificial Intelligence (AI), Machine Learning (ML), and digital-health technologies can assist in integrating genomic information with clinical variables and translating complex data into clinically useful information (Topol, 2019; Johnson *et al.*, 2021; Wang *et al.*, 2023).

Artificial Intelligence in Pharmacogenomic Data Analysis

AI can analyze large genomic and clinical datasets to identify patterns and associations relevant to drug response. Machine-learning models can incorporate genetic variants together with demographic, laboratory, disease, medication, and environmental information (Topol, 2019; Johnson *et al.*, 2021; Wang *et al.*, 2023).

Machine Learning for Predicting Drug Response

Supervised and unsupervised learning methods may assist in predicting drug response, toxicity, and treatment selection. Deep-learning approaches are particularly promising for integrating multimodal data, although clinical validation and interpretability remain essential before widespread adoption (Johnson *et al.*, 2021; Choi *et al.*, 2020).

Table 4: Major pharmacogenomic resources.

Resource	Primary role	Major contribution
CPIC	Clinical prescribing guidelines	Gene-specific therapeutic recommendations
DPWG	Pharmacogenomic guidelines	Genotype-based prescribing
PharmGKB	Knowledgebase	Clinical annotations and evidence
PharmVar	Pharmacogene nomenclature	Standardized star-allele definitions
PharmCAT	Clinical annotation software	Automated pharmacogenomic interpretation
FDA	Regulatory authority	Pharmacogenomic drug labeling
EMA	Regulatory authority	Biomarker-guided regulatory information

Table 5: Comparison of pharmacogenomic testing technologies.

Technology	Principle	Advantages	Limitations	Current use
PCR	Detection of predefined variants	Rapid, inexpensive	Limited variant coverage	Routine testing
Microarray	Multiplex predefined genotyping	High throughput	Cannot detect unrepresented variants	Pre-emptive testing
Targeted NGS	Sequencing selected pharmacogenes	Common and rare variant detection	Bioinformatics requirements	Increasing clinical adoption
WES	Coding-region sequencing	Broad variant detection	Limited regulatory coverage	Specialized use
WGS	Whole-genome sequencing	Comprehensive coverage	Cost and interpretation	Advanced precision medicine
Long-read sequencing	Long contiguous DNA reads	Structural variant/haplotype resolution	Higher cost and limited availability	Emerging
Multi-omics	Integrated molecular datasets	Broader biological characterization	Limited clinical validation	Primarily research

Clinical Decision Support Systems

Pharmacogenomic CDSS can retrieve stored genetic information when medications are prescribed and compare genotype information with evidence-based guidelines. Real-time alerts can recommend dose modification, alternative drugs, or additional monitoring (Hicks *et al.*, 2016; Bell *et al.*, 2014).

Electronic Health Records and Pre-emptive Pharmacogenomics

Because germline pharmacogenomic information generally remains stable throughout life, pre-emptive testing allows genetic information to be stored in electronic health records and reused whenever clinically relevant medications are prescribed (van der Wouden *et al.*, 2017; Rasmussen-Torvik *et al.*, 2014).

Emerging Digital Health Technologies

Cloud-based systems, secure genomic databases, federated learning, and other digital technologies may facilitate storage, sharing, and analysis of genomic data while addressing privacy and scalability challenges (Wang *et al.*, 2023; Kairouz *et al.*, 2021).

Future Perspectives

Important challenges for AI implementation include transparency, interpretability, external validation, data quality, cybersecurity, and regulatory oversight. AI should function as a clinical decision-support tool rather than a substitute for professional clinical judgment (Table 6).

Challenges and Limitations in Clinical Implementation

Despite substantial advances, clinical implementation remains inconsistent across healthcare systems. Scientific, technical, economic, educational, ethical, and regulatory barriers continue to limit routine use (van der Wouden *et al.*, 2017; Verbelen *et al.*, 2017; Dunnenberger and Cavallari, 2022).

Limited Clinical Evidence

Although many pharmacogenetic variants have been identified, only a subset has sufficient evidence for routine clinical implementation. Robust replication, multicenter studies, and clinical-outcome research remain necessary for many emerging gene-drug associations (Verbelen *et al.*, 2017; Tuteja *et al.*, 2022).

Ethnic Diversity and Population Representation

Underrepresentation of non-European populations in genomic research can limit the applicability of pharmacogenomic findings across diverse populations. Differences in allele frequencies and linkage patterns can influence the predictive performance of pharmacogenomic tests ((Petrovski and Goldstein, 2021; Popejoy and Fullerton, 2016).

Economic and Infrastructure Constraints

Testing costs, molecular diagnostic infrastructure, sequencing capacity, bioinformatics requirements, reimbursement policies, and availability of trained personnel can limit implementation, particularly in low- and middle-income settings (Veenstra *et al.*, 2000; Plumptre *et al.*, 2016).

Knowledge Gaps Among Healthcare Professionals

Limited pharmacogenomics education and confidence among healthcare professionals can impede appropriate interpretation and use of test results. Integration of pharmacogenomics into undergraduate and postgraduate education and continuing professional development is therefore important (Haga *et al.*, 2012; Murphy *et al.*, 2010).

Ethical, Legal, and Social Considerations

Pharmacogenomic testing raises concerns regarding privacy, informed consent, confidentiality, secondary use of genetic information, and potential discrimination. Appropriate governance and data-protection frameworks are necessary (Clayton *et al.*, 2019; McGuire and Burke, 2011).

Interpretation of Rare and Novel Variants

NGS increasingly identifies rare and previously uncharacterized variants. Many lack sufficient evidence to determine their functional or clinical significance and may therefore remain variants of uncertain significance (Ingelman-Sundberg *et al.*, 2018).

Table 6: Applications of AI in pharmacogenomics.

AI application	Function	Clinical significance
Machine learning	Predicts drug response from genomic and clinical data	Personalized drug selection
Deep learning	Identifies complex patterns	Precision oncology and prediction
Clinical decision support	Provides prescribing recommendations	Reduced medication errors
EHR integration	Stores and retrieves pharmacogenomic information	Pre-emptive prescribing
Cloud computing	Genomic data storage and sharing	Multi-center integration
Federated learning	Model development without centralized patient data	Improved privacy
Blockchain	Secure data management	Genomic-data governance

Table 7: Major challenges and potential solutions.

Challenge	Clinical impact	Potential solution
Limited evidence	Restricts implementation	Multicenter prospective studies
Population underrepresentation	Reduced applicability	Diverse genomic research
High testing cost	Limited accessibility	Cost reduction and reimbursement
Inadequate infrastructure	Delayed implementation	Molecular diagnostic investment
Limited clinician knowledge	Poor utilization	Curriculum and continuing education
Ethical/privacy concerns	Reduced public confidence	Governance and data protection
Rare variants	Uncertain significance	Functional studies and databases
Lack of standardization	Inconsistent recommendations	Harmonization and quality assurance

Standardization and Quality Assurance

Variation among laboratories in assay design, variant coverage, nomenclature, phenotype assignment, and reporting can result in inconsistent clinical interpretation. Standardized nomenclature, laboratory quality assurance, and harmonized reporting are essential (Pratt *et al.*, 2021).

Future Directions for Overcoming Barriers

Addressing these challenges requires collaboration among researchers, clinicians, pharmacists, geneticists, regulatory authorities, healthcare organizations, policymakers, and patients. Priorities include improving population representation, professional education, testing accessibility, reimbursement, laboratory infrastructure, and clinical decision-support integration (Table 7).

Pharmacogenomics in India: Current Status, Challenges, and Future Opportunities

India presents a particularly important setting for pharmacogenomics because of its extensive population diversity and the presence of numerous genetically distinct communities. Pharmacogenomic findings generated predominantly in European or other populations may not always be directly applicable to Indian populations (Ghosh and Sengupta, 2016; Indian Genome Variation Consortium, 2008; Thangaraj and Chaubey, 2009).

Genetic Diversity and Clinical Relevance

Variation in pharmacogenes including CYP2C19, CYP2C9, CYP2D6, CYP3A5, TPMT, NUDT15, SLCO1B1, and HLA genes has clinical implications for drug response in Indian populations. The distribution of clinically relevant variants may differ among population groups, emphasizing the need for representative Indian genomic datasets.

National Genomic Initiatives

The IndiGen initiative has generated a valuable resource of genetic variants from Indian genomes, while the GenomeIndia Project is developing a comprehensive catalogue of genetic diversity across

Indian populations. These resources can support discovery and interpretation of population-specific pharmacogenetic variation (Jain *et al.*, 2021; Bhattacharyya *et al.*, 2025).

Clinical Implementation in India

Clinical pharmacogenomic implementation in India remains limited and is concentrated mainly in selected academic centres, tertiary hospitals, and specialized laboratories. International recommendations such as CPIC and DPWG therefore remain important resources while Indian-specific evidence and implementation frameworks continue to develop.

Challenges Specific to India

Important barriers include unequal access to molecular diagnostic facilities, testing costs, limited availability of trained personnel, variable healthcare infrastructure, and limited integration of pharmacogenomics into healthcare education and prescribing systems. Locally generated clinical and economic evidence will be important for informing implementation and policy.

Future Opportunities

Future priorities include development of Indian-specific pharmacogenomic guidelines, integration of pharmacogenomics into pharmacy and medical education, establishment of accredited laboratories, expansion of electronic health-record infrastructure, and incorporation of pharmacogenomic decision support into clinical workflows (Table 8).

Future Perspectives

Pharmacogenomics has evolved from an experimental discipline into an important component of precision medicine. Continued advances in genomic technologies, computational biology, AI, and systems medicine may transform pharmacogenomics from a reactive clinical tool into a proactive strategy for individualized treatment (Mathur and Sutton, 2017; van der Wouden *et al.*, 2023; Wagner *et al.*, 2021).

Expansion of Pre-emptive Testing

Pre-emptive pharmacogenomic testing allows relevant genetic information to be generated before medication exposure and

Table 8: Current status and future priorities in India.

Domain	Current status	Future priority
Population genomics	Expanding through national initiatives	Comprehensive population representation
Clinical implementation	Limited to selected centers	Broader healthcare integration
Guidelines	Predominantly international	Indian-specific recommendations
Laboratory infrastructure	Uneven	Accredited molecular laboratories
Professional education	Limited formal training	Curriculum integration
Health informatics	Variable EHR adoption	Pharmacogenomic CDSS
Research	Increasing genomic studies	Multicenter implementation trials

Table 9: Future directions.

Emerging area	Expected impact
Pre-emptive pharmacogenomics	Lifelong availability of actionable genetic information
Whole-genome sequencing	Comprehensive identification of genomic variation
Long-read sequencing	Improved structural-variant and haplotype characterization
Multi-omics	Enhanced prediction beyond genomics alone
Artificial intelligence	Advanced predictive treatment models
EHR integration	Automated real-time decision support
Global genomic databases	Improved interpretation across populations
Precision therapeutics	Integrated individualized treatment

stored for future clinical use. The PREPARE/U-PGx experience provides important evidence that pre-emptive pharmacogenomic testing can be implemented across healthcare systems (van der Wouden *et al.*, 2023; Van Driest *et al.*, 2014).

Whole-Genome Pharmacogenomics

Future testing may move beyond selected pharmacogenes toward comprehensive genomic profiling. Whole-genome sequencing can identify coding and non-coding variants, structural variation, and other genomic features that may contribute to drug response, although interpretation remains challenging (Wagner *et al.*, 2021; Ashley, 2016).

Integration of Multi-Omics

Drug response is influenced by dynamic biological processes in addition to inherited genetic variation. Integration of genomics with transcriptomics, epigenomics, proteomics, metabolomics, microbiome data, and other molecular information may improve characterization of treatment response (Hasin *et al.*, 2017; Karczewski and Snyder, 2018).

Artificial Intelligence and Predictive Precision Medicine

AI and ML may assist in integrating genomic information with EHR data, laboratory findings, imaging, and other clinical variables to predict treatment response and toxicity. Explainability, external validation, transparency, and regulatory oversight will remain essential (Rajkomar *et al.*, 2019; Topol, 2019).

Global Collaboration and Standardization

International collaboration will be necessary to harmonize laboratory methodologies, nomenclature, phenotype classification, reporting, and clinical guidelines. Genomic databases representing diverse populations will improve variant interpretation and reduce disparities associated with population underrepresentation.

Toward Precision Therapeutics

The future of pharmacogenomics extends beyond prediction based solely on inherited variants toward integrated precision therapeutics. Genetic, molecular, clinical, environmental, and behavioral information may increasingly be combined to support individualized treatment decisions. Continued innovation, evidence generation, education, ethical governance, and equitable implementation will determine how successfully these technologies translate into routine patient care (Table 9).

CONCLUSION

Pharmacogenomics has emerged as an important component of precision medicine and has challenged the traditional one-size-fits-all approach to pharmacotherapy. By identifying genetic variation that influences drug metabolism, transport, target sensitivity, and immune-mediated toxicity, pharmacogenomics can support individualized drug selection and dosing and can prevent selected serious adverse drug reactions.

The strongest clinical applications currently involve well-established gene-drug pairs such as CYP2C19-clopidogrel, DPYD-fluoropyrimidines, TPMT/NUDT15-thiopurines, SLCO1B1-statins, CYP3A5-tacrolimus, and selected HLA-associated drug hypersensitivity reactions. Evidence-based recommendations from CPIC and DPWG, together with

resources such as PharmGKB and PharmVar, have facilitated translation of genomic findings into clinical practice.

Technological advances in PCR-based testing, microarrays, NGS, long-read sequencing, electronic health records, clinical decision support, and artificial intelligence are expected to further expand the clinical utility of pharmacogenomics. At the same time, challenges involving evidence quality, population diversity, cost, infrastructure, professional education, privacy, rare-variant interpretation, and standardization must be addressed.

India represents an important opportunity because of its extensive genetic diversity and expanding national genomic initiatives. Development of representative Indian genomic resources and population-specific clinical evidence will be essential for equitable implementation.

Ultimately, pharmacogenomics should be viewed not as a replacement for clinical judgment but as an additional evidence-based tool for individualized therapeutic decision-making. Continued scientific innovation, rigorous clinical validation, multidisciplinary collaboration, and equitable implementation will be essential for realizing the potential of pharmacogenomics to improve medication safety, therapeutic effectiveness, and patient-centered care.

ABBREVIATIONS

ADR: Adverse Drug Reaction; **CYP450:** Cytochrome P450; **GWAS:** Genome-Wide Association Study; **NGS:** Next-Generation Sequencing; **WES:** Whole-Exome Sequencing; **WGS:** Whole-Genome Sequencing; **CDSS:** Clinical Decision Support System; **AI:** Artificial Intelligence; **ML:** Machine Learning; **EHR:** Electronic Health Record; **CPIC:** Clinical Pharmacogenetics Implementation Consortium; **DPWG:** Dutch Pharmacogenetics Working Group; **SJS/TEN:** Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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