

Pharmacogenomics-driven precision pharmacy: Mechanisms, challenges, and translational advances

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Abstract

Pharmacogenomics represents a transformative paradigm in clinical pharmacology, offering the promise of individualized drug therapy based on genetic profiles. This comprehensive review examines the mechanisms underlying pharmacogenomic variability, the current state of clinical implementation, and the translational advances driving precision pharmacy practice. We systematically discuss the role of pharmacokinetic genes, including cytochrome P450 enzymes (CYP2D6, CYP2C19, CYP2C9, CYP3A4/5), thiopurine S-methyltransferase (TPMT), and solute carrier organic anion transporter family member 1B1 (SLCO1B1), as well as pharmacodynamic targets such as vitamin K epoxide reductase complex subunit 1 (VKORC1) and adrenoceptor beta 1 (ADRB1). Human leukocyte antigen (HLA) genes and their association with severe adverse drug reactions are also critically evaluated. The review further explores the evidence base supporting clinical pharmacogenomic implementation, including guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), and major implementation initiatives such as the IGNITE network and the PREPARE study. We examine the integration of artificial intelligence and machine learning approaches for pharmacogenomic prediction, the emergence of polygenic risk scores, and the role of multi-omics integration in refining therapeutic decision-making. Challenges, including economic barriers, regulatory considerations, health equity concerns, and healthcare system integration, are thoroughly discussed. Finally, we outline future directions for the field, emphasizing the need for global diversification of pharmacogenomic data, enhanced clinical decision support systems, and policy frameworks that facilitate equitable access to precision pharmacy services.

Keywords: precision pharmacy, CYP450, personalized medicine, clinical pharmacology, polygenic risk scores.

Farmácia de precisão baseada em farmacogenômica: Mecanismos, desafios e avanços translacionais

Resumo

A farmacogenômica representa um paradigma transformador na farmacologia clínica, oferecendo a promessa de uma terapia medicamentosa individualizada com base nos perfis genéticos dos pacientes. Esta revisão abrangente examina os mecanismos subjacentes à variabilidade farmacogenômica, o estado atual da implementação clínica e os avanços translacionais que impulsionam a prática da farmácia de precisão. São discutidos de forma sistemática os papéis dos genes envolvidos na farmacocinética, incluindo as enzimas do

citocromo P450 (CYP2D6, CYP2C19, CYP2C9 e CYP3A4/5), a tiopurina S-metiltransferase (TPMT) e o transportador de ânions orgânicos da família solute carrier 1B1 (SLCO1B1), bem como os alvos farmacodinâmicos, como a subunidade 1 do complexo da vitamina K epóxido redutase (VKORC1) e o receptor beta-1 adrenérgico (ADRB1). Os genes do sistema de antígenos leucocitários humanos (HLA) e sua associação com reações adversas graves a medicamentos também são avaliados criticamente. A revisão explora ainda as evidências que sustentam a implementação clínica da farmacogenômica, incluindo as diretrizes do Clinical Pharmacogenetics Implementation Consortium (CPIC), do Dutch Pharmacogenetics Working Group (DPWG) e importantes iniciativas de implementação, como a rede IGNITE e o estudo PREPARE. Também são examinados a integração de abordagens baseadas em inteligência artificial e aprendizado de máquina para predição farmacogenômica, o surgimento dos escores de risco poligênico e o papel da integração de dados multiômicos no aprimoramento da tomada de decisão terapêutica. Desafios relacionados a barreiras econômicas, aspectos regulatórios, equidade em saúde e integração aos sistemas de saúde são discutidos de maneira abrangente. Por fim, são apresentadas perspectivas futuras para a área, enfatizando a necessidade de maior diversificação global dos dados farmacogenômicos, do aprimoramento dos sistemas de suporte à decisão clínica e do desenvolvimento de políticas públicas que promovam o acesso equitativo aos serviços de farmácia de precisão.

Palavras-chave: farmácia de precisão, CYP450, medicina personalizada, farmacologia clínica, escores de risco poligênico.

1. Introduction

The intersection of genomics and clinical pharmacology has given rise to pharmacogenomics, a discipline that seeks to elucidate how genetic variation influences individual drug response. Since the landmark discovery of inherited differences in drug acetylation by Motulsky in 1957 and the subsequent molecular characterization of cytochrome P450 enzyme polymorphisms in the 1980s, the field has evolved from observational studies of familial drug response patterns to a sophisticated, evidence-based clinical science (Gonzalez et al., 1988; Motulsky, 1957). The completion of the Human Genome Project in 2003 catalyzed exponential growth in pharmacogenomic discovery, enabling genome-wide association studies (GWAS) that have identified thousands of genetic variants associated with drug response phenotypes (International Human Genome Sequencing Consortium, 2004).

Pharmacogenomics holds particular promise for precision pharmacy, defined as the application of genomic and other biomarker information to optimize medication selection, dosing, and monitoring for individual patients. The conceptual framework for precision pharmacy builds upon the recognition that drug response is a complex trait influenced by multiple genetic and non-genetic factors. Inter-individual variability in pharmacokinetics and pharmacodynamics can result in therapeutic failure or severe adverse drug reactions (ADRs), which remain a leading cause of morbidity and mortality worldwide. ADRs account for approximately 6.5% of hospital admissions in developed countries and represent a substantial burden on healthcare systems, with annual costs exceeding \$30 billion in the United States alone (Pirmohamed et al., 2004; Sultana et al., 2013).

The clinical translation of pharmacogenomics has been facilitated by international consortia, most notably the Clinical Pharmacogenetics Implementation Consortium (CPIC), established in 2009 to develop evidence-based guidelines for gene-drug pairs with sufficient scientific evidence to support clinical actionability (Relling et al., 2011). As of 2024, CPIC has published guidelines for more than 25 gene-drug pairs, providing standardized recommendations for genotype-based therapeutic adjustments. Complementary efforts by the Dutch Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety, and the European Pharmacogenomics Implementation Consortium (EU-PACT) have further advanced the global standardization of pharmacogenomic clinical practice (Swen et al., 2011).

Despite remarkable progress in pharmacogenomic discovery and guideline development, significant challenges persist in translating research findings into routine clinical practice. Barriers include limited provider education, inadequate electronic health record (EHR) integration, reimbursement complexities, and concerns about health equity in the context of predominantly European-ancestry pharmacogenomic datasets (Sirugo et al., 2019). Furthermore, the emergence of artificial intelligence (AI) and machine learning (ML) approaches, polygenic risk scores (PRS), and multi-omics integration presents both opportunities and new complexities for precision pharmacy implementation.

This comprehensive review provides a critical examination of the mechanisms underlying pharmacogenomic variation, the current evidence base for clinical implementation, emerging translational technologies, and the challenges facing widespread adoption of precision pharmacy services. We aim to synthesize the current state of

the field, identify gaps in knowledge and practice, and outline future directions for advancing pharmacogenomics-driven precision pharmacy across diverse healthcare settings. In Figure 1, we provide an overview of pharmacogenomic mechanisms in precision pharmacy.

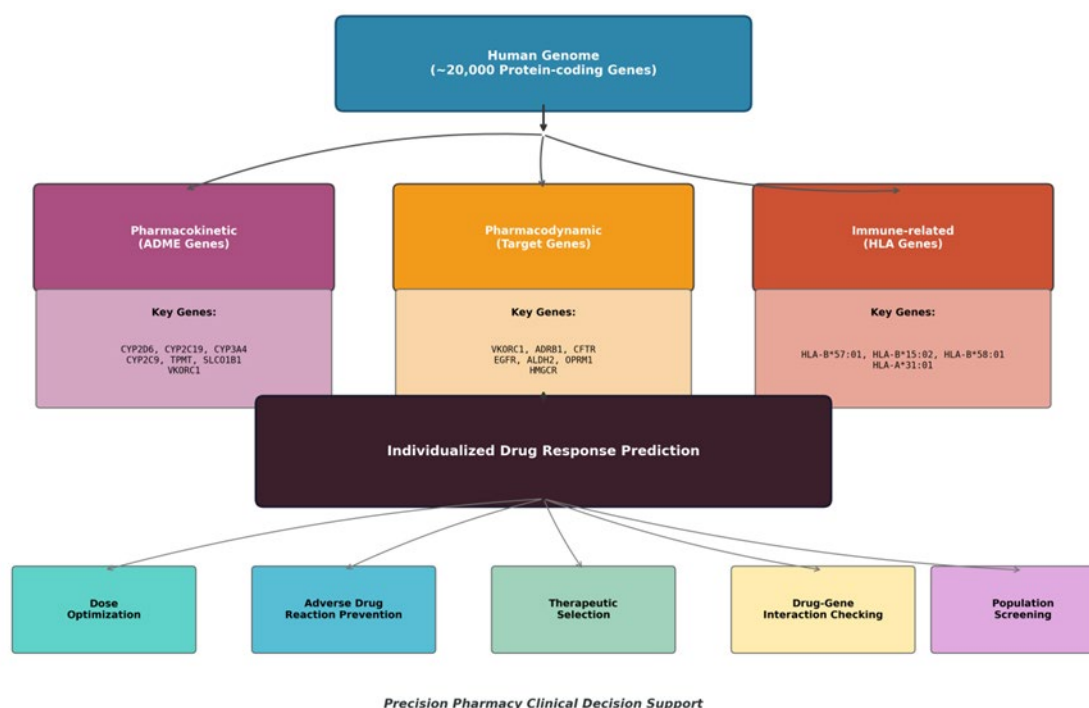


Figure 1. Overview of pharmacogenomic mechanisms in precision pharmacy. Genetic variation in pharmacokinetic (ADME), pharmacodynamic, and immune-related genes influences individual drug response, enabling personalized therapeutic strategies including dose optimization, adverse drug reaction prevention, and therapeutic selection. Source: Authors, 2026.

2. Literature Search Strategy

This review was conducted as a narrative review aimed at summarizing the current evidence regarding pharmacogenomics-driven precision pharmacy. Scientific literature was identified through comprehensive searches in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar. The literature search emphasized recent publications (2015–2026), while landmark studies, pivotal clinical trials, and foundational guidelines published before 2015 were intentionally included to provide historical context and support key concepts in pharmacogenomics and precision pharmacy.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators (AND/OR). Search terms included pharmacogenomics, precision pharmacy, precision medicine, pharmacogenetics, CYP450, CPIC, DPWG, polygenic risk scores, artificial intelligence, clinical implementation, and personalized medicine.

Priority was given to systematic reviews, meta-analyses, randomized controlled trials, international clinical guidelines, consensus statements, and high-impact original research articles. Additional relevant studies were identified through manual screening of the reference lists of selected publications.

The retrieved literature was critically evaluated according to its scientific relevance, consistency of evidence, methodological rigor, and contribution to advancing knowledge in pharmacogenomics and precision pharmacy. As this study was designed as a narrative review, formal systematic review procedures, including PRISMA flow diagrams and structured risk-of-bias assessment, were not applied.

3. Pharmacogenomic Mechanisms in Drug Response

The mechanistic basis of pharmacogenomics encompasses genetic variation across multiple categories of genes that influence drug disposition and action. These include pharmacokinetic genes involved in drug absorption, distribution, metabolism, and excretion (ADME); pharmacodynamic genes encoding drug targets; and immune-related genes, particularly those within the human leukocyte antigen (HLA) complex, that mediate idiosyncratic adverse drug reactions. Understanding the molecular mechanisms by which genetic variants alter protein function and, consequently, drug response is essential for the rational application of pharmacogenomics in clinical practice.

3.1 Pharmacokinetic genes: The ADME paradigm

The cytochrome P450 (CYP450) superfamily of heme-thiolate enzymes catalyzes the oxidative metabolism of approximately 75% of all clinically used drugs. Among the 57 functional CYP genes in humans, six isoforms (CYP3A4, CYP3A5, CYP2D6, CYP2C9, CYP2C19, and CYP1A2) account for the metabolism of over 90% of CYP450-mediated drug biotransformations (Zanger; Schwab, 2013). Genetic polymorphisms in these genes can profoundly alter enzyme activity, resulting in distinct metabolizer phenotypes: poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NM), rapid metabolizers (RM), and ultra-rapid metabolizers (UM).

CYP2D6 represents one of the most extensively studied pharmacogenes, with over 150 identified allelic variants. The gene exhibits extensive structural variation, including gene duplications, deletions, and rearrangements that contribute to its remarkable inter-individual variability. CYP2D6 metabolizes approximately 25% of clinically used drugs, including codeine, tramadol, tamoxifen, various antidepressants, and antipsychotics (Zhou, 2009). The clinical implications of CYP2D6 polymorphism are exemplified by codeine pharmacotherapy: the prodrug requires CYP2D6-mediated O-demethylation to morphine for analgesic effect. CPIC guidelines recommend avoiding codeine in CYP2D6 poor metabolizers due to lack of efficacy and in ultra-rapid metabolizers due to increased risk of opioid toxicity, particularly in pediatric populations (Crews et al., 2014).

CYP2C19 polymorphisms significantly impact the efficacy of clopidogrel, a widely prescribed antiplatelet agent. Clopidogrel is a prodrug requiring CYP2C19-mediated bioactivation to its active metabolite. Loss-of-function alleles, particularly CYP2C19*2 and *3, impair this activation, resulting in reduced antiplatelet response and increased risk of adverse cardiovascular events in patients undergoing percutaneous coronary intervention. The landmark TRITON-TIMI 38 trial and subsequent meta-analyses demonstrated that carriers of CYP2C19 loss-of-function alleles had a 30-50% increased risk of major adverse cardiovascular events compared to non-carriers (Mega et al., 2009). CPIC guidelines recommend alternative antiplatelet agents, such as prasugrel or ticagrelor, for CYP2C19 intermediate and poor metabolizers undergoing percutaneous coronary intervention.

CYP2C9 and VKORC1 polymorphisms are critical determinants of warfarin dose requirements. Warfarin, a vitamin K antagonist used for anticoagulation in atrial fibrillation and venous thromboembolism, has a narrow therapeutic index and exhibits 10-20 fold inter-individual variability in dose requirements. The IWPC (International Warfarin Pharmacogenetics Consortium) and GAGE (Genetic Attributes and Warfarin Response) studies demonstrated that pharmacogenetic algorithms incorporating CYP2C9 and VKORC1 genotypes, along with clinical factors, explained approximately 50-55% of dose variability, compared to 20-25% for clinical factors alone (IWPC, 2009). The FDA-approved warfarin label includes genotype-guided dosing recommendations, and multiple randomized controlled trials have demonstrated the superiority of pharmacogenetic-guided warfarin dosing during initiation.

CYP3A4 and CYP3A5, the most abundant hepatic CYP enzymes, metabolize approximately 37% of clinically used drugs, including immunosuppressants (tacrolimus, cyclosporine), statins (atorvastatin, simvastatin), calcium channel blockers, and many chemotherapeutic agents. The CYP3A5*3 allele (rs776746), which creates an aberrant splice site, is the most important functional variant, with allele frequencies varying dramatically across populations (5-15% in Europeans vs. 60-90% in sub-Saharan Africans). CYP3A5 expressers require 1.5-2 fold higher tacrolimus doses to achieve therapeutic concentrations, and CPIC guidelines provide genotype-based dosing recommendations for tacrolimus in solid organ transplant recipients (Birdwell et al., 2015).

Beyond CYP450 enzymes, pharmacogenomic variation in drug transporters significantly influences drug disposition. SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1), which mediates hepatic uptake of statins. The SLCO1B1*5 allele (rs4149056, V174A) reduces transporter activity, increasing systemic exposure to simvastatin and other statins and predisposing carriers to statin-induced myopathy. The SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial demonstrated that SLCO1B1*5 carriers had a 4.5-fold increased risk of simvastatin-induced myopathy (Link et

al., 2008). CPIC guidelines recommend considering lower simvastatin doses or alternative statins for SLCO1B1 variant carriers.

3.2 Pharmacodynamic genes

Pharmacodynamic genes encode proteins that mediate drug therapeutic effects, and genetic variation in these targets can alter drug sensitivity and efficacy. VKORC1, the molecular target of warfarin, exhibits common polymorphisms (rs9923231, rs9934438) that significantly influence warfarin sensitivity. The VKORC1 -1639G>A variant (rs9923231) alters a transcription factor binding site, reducing VKORC1 expression and resulting in lower warfarin dose requirements. This variant demonstrates marked population differentiation, with allele frequencies ranging from 10% in African populations to 80-90% in Asian populations, contributing to observed racial differences in warfarin dosing (Limdi et al., 2010).

ADRB1 (beta-1 adrenergic receptor) polymorphisms, particularly Arg389Gly (rs1801253), influence response to beta-blockers in heart failure and hypertension. The Arg389 variant demonstrates enhanced G-protein coupling and signaling, and clinical studies suggest that Arg389 homozygotes derive greater benefit from beta-blocker therapy, particularly carvedilol and metoprolol, compared to Gly389 carriers (Liggett et al., 2006). However, the clinical utility of ADRB1 genotyping remains debated, as prospective randomized trials have yielded inconsistent results regarding the incremental value of genotype-guided beta-blocker selection.

OPRM1 (mu-opioid receptor) polymorphisms, particularly the Asn40Asp variant (rs1799971, A118G), have been extensively studied in the context of opioid analgesia. The 118G allele alters receptor glycosylation and binding affinity for beta-endorphin, potentially influencing opioid dose requirements. Meta-analyses suggest that 118G carriers may require higher morphine doses for adequate pain control, though effect sizes are modest and clinical implementation has been limited by heterogeneous study designs and outcomes (Lotsch; Geisslinger, 2005).

3.3 Human leukocyte antigen genes and idiosyncratic drug reactions

The HLA gene complex on chromosome 6 encodes highly polymorphic cell surface proteins critical for antigen presentation to T lymphocytes. Specific HLA alleles are strongly associated with severe idiosyncratic adverse drug reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). These associations are characterized by strong effect sizes (odds ratios often >100) and high specificity, making HLA screening among the most clinically actionable applications of pharmacogenomics (Phillips et al., 2018).

The association between HLA-B*57:01 and abacavir hypersensitivity represents one of the most successful examples of pharmacogenomic implementation. Abacavir, a nucleoside reverse transcriptase inhibitor used in HIV therapy, causes a potentially fatal hypersensitivity reaction in 5-8% of patients. The PREDICT-1 prospective randomized trial demonstrated that HLA-B*57:01 screening, with exclusion of carriers from abacavir therapy, essentially eliminated immunologically confirmed hypersensitivity reactions (Mallal et al., 2008). This testing is now the standard of care globally and is required by regulatory agencies before abacavir initiation.

HLA-B*15:02 screening before carbamazepine prescription has been implemented in multiple Asian countries following the identification of this allele as a major risk factor for carbamazepine-induced SJS/TEN in populations of Han Chinese and Southeast Asian ancestry. The FDA and EMA have updated carbamazepine labeling to recommend HLA-B*15:02 screening in at-risk populations, with testing widely available in Taiwan, Hong Kong, Singapore, Thailand, and Malaysia (Chen et al., 2011). Similarly, HLA-B*58:01 is associated with allopurinol-induced severe cutaneous adverse reactions, and HLA-A*31:01 with carbamazepine-induced DRESS in European populations.

The molecular mechanisms underlying HLA-drug associations involve the altered peptide repertoire model, in which drug or drug metabolite binding modifies peptide presentation by specific HLA alleles, triggering aberrant T-cell responses. Recent structural studies have provided insights into these interactions, including the characterization of abacavir binding to the HLA-B*57:01 peptide-binding groove, which alters the repertoire of presented peptides (Illing et al., 2012). These mechanistic insights may facilitate the prediction of HLA-associated drug toxicities and the development of safer therapeutic alternatives. In Figure 2, we analyze pharmacokinetic genes and their clinical impact on drug therapy.

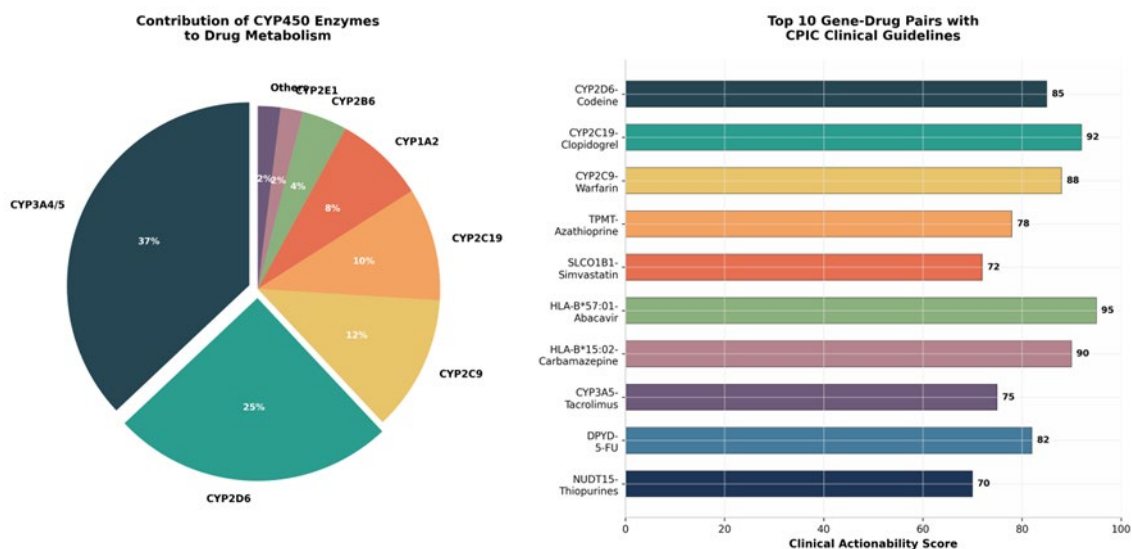


Figure 2. Pharmacokinetic genes and their clinical impact on drug therapy. (A) Contribution of individual CYP450 enzymes to drug metabolism. (B) Top 10 gene-drug pairs with established CPIC clinical guidelines, ranked by clinical actionability score. Source: Authors, 2026.

3.4 Summary of key pharmacogenomic gene-drug interactions

Table 1 summarizes the most clinically significant pharmacogenomic gene-drug interactions with established CPIC guidelines, including affected genes, relevant drugs, metabolizer phenotypes, clinical consequences, and therapeutic recommendations.

Table 1. Key pharmacogenomic gene-drug interactions with CPIC clinical guidelines.

Gene	Drug	Phenotype	Clinical Consequence	CPIC Recommendation
CYP2D6	Codeine	PM, UM	Toxicity or lack of efficacy	Avoid codeine; use alternative analgesics
CYP2C19	Clopidogrel	IM, PM	Reduced antiplatelet effect	Use prasugrel or ticagrelor
CYP2C9/VKORC1	Warfarin	Multiple	Bleeding or thrombosis	Genotype-guided dosing algorithm
TPMT/NUDT15	Azathioprine	IM, PM	Myelosuppression	Reduce starting dose by 30-90%
SLCO1B1	Simvastatin	*5 carriers	Myopathy risk	Lower dose or alternative statin
HLA-B*57:01	Abacavir	Positive	Hypersensitivity reaction	Contra indicated; use an alternative
HLA-B*15:02	Carbamazepine	Positive	SJS/TEN risk	Contra indicated in Asian ancestry
CYP3A5	Tacrolimus	Non-expresser	Nephrotoxicity risk	Higher initial dosing is required

Gene	Drug	Phenotype	Clinical Consequence	CPIC Recommendation
DPYD	5-Fluorouracil	PM	Severe toxicity	Avoid or strongly reduce the dose

Source: Authors, 2026.

4. Clinical Implementation and Evidence Base

The translation of pharmacogenomic discoveries into clinical practice requires robust evidence of clinical validity, clinical utility, and cost-effectiveness. Over the past two decades, a substantial body of evidence has accumulated supporting the clinical implementation of pharmacogenomic testing across multiple therapeutic areas. This section reviews the major guideline consortia, key clinical trials, and implementation programs that have shaped the current landscape of precision pharmacy.

4.1 Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

CPIC was established in 2009 as a collaborative effort between the National Institutes of Health (NIH) Pharmacogenomics Research Network and PharmGKB to develop peer-reviewed, evidence-based guidelines for gene-drug pairs with sufficient scientific evidence to support clinical actionability. CPIC guidelines follow a standardized development process involving systematic literature review, standardized evidence grading, and expert consensus to provide gene-based therapeutic recommendations (Relling; Klein, 2011).

As of 2024, CPIC has published guidelines for more than 25 gene-drug pairs, encompassing medications used in cardiovascular disease (warfarin, clopidogrel, simvastatin), psychiatry (antidepressants, antipsychotics), oncology (tamoxifen, thiopurines, 5-fluorouracil), infectious disease (abacavir, efavirenz, voriconazole), pain management (codeine, tramadol, opioids), and transplantation (tacrolimus, azathioprine). CPIC guidelines are updated periodically to incorporate new evidence, and the consortium actively engages with regulatory agencies, professional societies, and EHR vendors to facilitate implementation (Caudle et al., 2017).

The Dutch Pharmacogenetics Working Group (DPWG) provides complementary guidelines that are widely adopted in European countries. DPWG guidelines differ from CPIC in their emphasis on providing therapeutic alternatives for patients with actionable genotypes, and they have developed an extensive set of recommendations integrated into Dutch clinical decision support systems (Swen et al., 2011). The harmonization of CPIC and DPWG guidelines has been an important development, with ongoing efforts to align recommendations and reduce confusion among clinicians.

4.2 Evidence from randomized controlled trials

Multiple randomized controlled trials (RCTs) have evaluated the clinical utility of pharmacogenomic-guided therapy across various specialties. The GIFT (Genetics Informatics Trial) of warfarin therapy demonstrated that genotype-guided warfarin dosing significantly improved the percentage of time in the therapeutic INR range during the first four weeks of therapy compared to clinical dosing (62.8% vs. 59.1%, $p = 0.007$) (Gage et al., 2017). The PHARMACogenomic determination of Clopidogrel effectiveness (PHARMCLO) trial showed that CYP2C19 genotype-guided selection of P2Y12 inhibitors reduced the composite endpoint of major adverse cardiovascular events in patients with acute coronary syndrome compared to standard clopidogrel therapy.

In psychiatry, the PRIME Care (Precision Medicine in Mental Health Care) trial evaluated pharmacogenomic testing for antidepressant and antipsychotic prescribing in veterans. While the primary outcome of remission at 12 weeks did not differ significantly between genotype-guided and usual care groups, significant benefits were observed in prespecified subgroups and secondary outcomes, including reduced symptom severity and fewer antidepressant prescriptions (Oslin et al., 2024). The TARGET (Treatment Guided by Genotyping) study demonstrated that CYP2D6/CYP2C19 genotype-guided antidepressant therapy resulted in higher response rates compared to standard care in patients with major depressive disorder.

The PREPARE (Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions) study, conducted across seven European countries, evaluated the impact of preemptive pharmacogenomic panel testing on clinically relevant adverse drug reactions. Results demonstrated that genotype-guided prescribing significantly reduced the occurrence of ADRs across 12 actionable gene-drug pairs, with a number needed to

genotype of approximately 20 to prevent one ADR (Sven et al., 2023). The PHGKB (Public Health Genomics and Precision Health Knowledge Base) meta-analyses have further supported the clinical utility of pharmacogenomic testing across multiple gene-drug pairs.

4.3 Major implementation initiatives

The IGNITE (Implementing Genomics in Practice) Network, funded by the National Human Genome Research Institute (NHGRI), has been instrumental in advancing pharmacogenomic implementation science in the United States. IGNITE consists of multiple clinical and research sites that have developed and evaluated strategies for integrating genomic medicine into diverse healthcare settings. Key contributions include the development of implementation frameworks, EHR integration tools, provider education resources, and patient-facing materials (Weitzel et al., 2016).

The Vanderbilt University Medical Center's PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment) program represents one of the longest-running preemptive pharmacogenomic implementation programs. Since its inception in 2010, PREDICT has genotyped over 100,000 patients for a panel of pharmacogenes, with results stored in the EHR and surfaced through clinical decision support at the point of prescribing. Program evaluations have demonstrated high clinician acceptance, significant reductions in ADRs for actionable gene-drug pairs, and favorable cost-effectiveness estimates (Van Driest et al., 2014).

The St. Jude Children's Research Hospital PG4KDS (Pharmacogenetics for Kids) program pioneered preemptive pharmacogenomic testing in pediatric populations, genotyping over 1,000 children for 230 pharmacogenetic variants. The program demonstrated the feasibility of preemptive testing in children, the clinical utility of pharmacogenomic results across multiple specialties, and the importance of family-centered communication about pharmacogenomic findings (Hoffman et al., 2014).

Internationally, the Ubiquitous Pharmacogenomics (U-PGx) consortium has implemented preemptive pharmacogenomic testing across healthcare systems in seven European countries, while the PREPARE study has established frameworks for population-level pharmacogenomic screening. In Asia, the Pharmacogenomics Research Network for Preemptive Pharmacogenomics in Asia (PROMPT-Asia) has addressed the critical need for population-specific pharmacogenomic data and implementation strategies tailored to diverse Asian populations. In Figure 3, we put the timeline of key milestones in pharmacogenomics implementation.

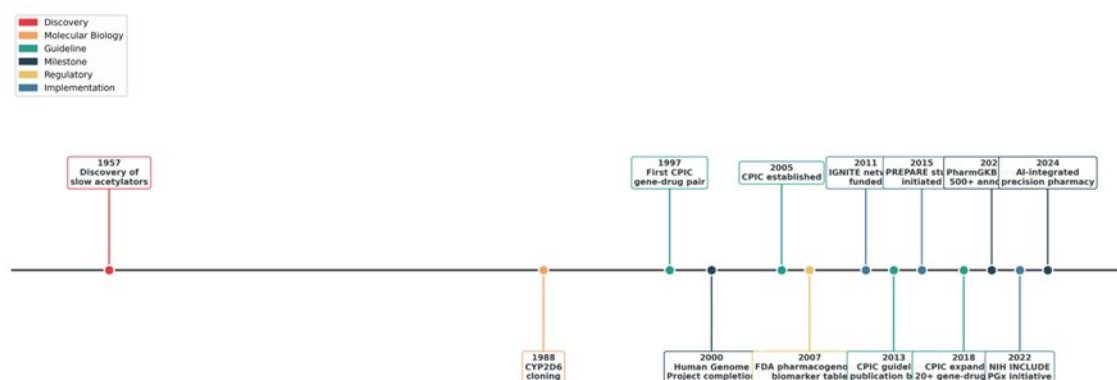


Figure 3. Timeline of key milestones in pharmacogenomics implementation. The field has evolved from early observations of inherited drug response variation through molecular characterization, guideline development, and large-scale clinical implementation programs. Source: Authors, 2026.

4.4 Summary of major pharmacogenomic implementation programs

Table 2. Major pharmacogenomic implementation programs worldwide.

Program	Country/Region	Type	Key Features
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Program	Country/Region	Type	Key Features
PREDICT	USA (Vanderbilt)	Preemptive	100,000+ genotyped; EHR CDS integration
PREPARE	Europe (7 countries)	Preemptive	Population-level preemptive testing
PG4KDS	USA (St. Jude)	Preemptive	Pediatric pharmacogenomics pioneer
IGNITE Network	USA (Multi-site)	Implementation	Implementation Science Research Network
U-PGx	Europe (Multi-site)	Implementation	Cost-effectiveness evaluation
PROMPT-Asia	Asia (Multi-site)	Research	Population-specific PGx data
PRIME Care	USA (VA System)	RCT	Veterans pharmacogenomics trial

Source: Authors, 2026.

5. Precision Pharmacy Practice Models

The clinical implementation of pharmacogenomics requires structured practice models that integrate genetic testing, clinical decision support, and patient care workflows. Three primary models have emerged: reactive genotyping, in which testing is ordered in response to specific prescribing decisions; preemptive genotyping, in which patients are screened for pharmacogenetic variants before they are needed for clinical decision-making; and point-of-care testing, which enables rapid genetic analysis at the site of clinical care. Each model has distinct advantages, limitations, and optimal applications.

5.1 Preemptive pharmacogenomic testing

Preemptive pharmacogenomic testing, also known as pre-prescription or prospective genotyping, involves the analysis of a panel of pharmacogenes in anticipation of future prescribing needs. This model offers several theoretical advantages over reactive testing: results are available at the point of prescribing without delays associated with test ordering and result reporting; patients can be educated about their pharmacogenomic profile before medication decisions are needed; and the per-gene cost of panel testing is typically lower than single-gene testing (Bousman et al., 2023).

The optimal gene panel for preemptive testing remains a subject of ongoing discussion. Most implementation programs utilize panels of 10-20 genes covering medications commonly prescribed in their patient populations. The CPIC gene list includes CYP2D6, CYP2C19, CYP2C9, CYP3A5, SLCO1B1, TPMT, NUDT15, DPYD, VKORC1, CYP2B6, and HLA-B genes, among others. The selection of genes for inclusion should be based on the strength of evidence for clinical actionability, the prevalence of actionable variants in the target population, and the frequency of use of affected medications.

The PREPARE study demonstrated the feasibility of preemptive pharmacogenomic testing at a population level across diverse European healthcare systems. In this study, approximately 7% of participants carried at least one actionable pharmacogenetic variant, and genotype-guided prescribing significantly reduced ADR rates. Cost-effectiveness analyses have generally favored preemptive testing in settings with high medication utilization, with incremental cost-effectiveness ratios within acceptable thresholds when testing costs are below \$250-500 per patient (Verbelen et al., 2017).

5.2 Electronic health record integration and clinical decision support

Effective EHR integration is essential for the successful implementation of pharmacogenomics at scale. Clinical decision support (CDS) systems that alert providers to gene-drug interactions at the point of prescribing have been the primary mechanism for translating pharmacogenomic test results into clinical action. Key requirements

for effective pharmacogenomic CDS include: automated matching of genetic results to prescribed medications; tiered alerting that minimizes alert fatigue; clear, actionable recommendations linked to evidence-based guidelines; and documentation tools that facilitate informed clinical decision-making (Pulley et al., 2012).

The HL7 FHIR (Fast Healthcare Interoperability Resources) standard has emerged as a critical enabler for pharmacogenomic data exchange. The Genomics Operations (GenO) specification defines FHIR profiles for pharmacogenomic test results, enabling interoperable data sharing between laboratories, EHR systems, and clinical decision support tools. The SMART on FHIR platform allows pharmacogenomic applications to be embedded within EHR workflows, providing guideline recommendations directly within the prescribing interface.

Despite technological advances, significant challenges remain in EHR integration. Many healthcare systems utilize legacy EHR platforms with limited genomic data capabilities. The complexity of pharmacogenomic data, including diploidy calling, phenotype assignment, and allele definitions, requires specialized clinical decision support that is not universally available. Furthermore, the need for continuous updating of guidelines and allele definitions poses ongoing maintenance challenges for CDS systems.

5.3 Multi-omics integration in precision pharmacy

While pharmacogenomics focuses on germline genetic variation, the integration of additional omics data layers promises to refine therapeutic prediction beyond what is achievable with genomics alone. Transcriptomics, metabolomics, epigenomics, and proteomics each provide complementary information about drug response that is not captured by DNA sequence variation alone.

Transcriptomic profiling through RNA sequencing can capture the dynamic regulation of drug-metabolizing enzymes and transporters, providing a functional readout that integrates genetic and environmental influences on gene expression. The concept of a "pharmacotranscriptome" has emerged, in which baseline gene expression patterns predict drug response. In oncology, tumor transcriptomic profiling is already standard practice for guiding targeted therapy selection, and similar approaches are being explored for pharmacogenomic applications (Basile; Ritchie, 2018).

The gut microbiome has emerged as an important modifier of drug response, with microbial enzymes contributing to the metabolism of numerous drugs. The cardiac glycoside digoxin provides a classic example: the gut bacterium *Eggerthella lenta* reduces digoxin to its inactive metabolite dihydrodigoxin, and patients colonized with high levels of this organism exhibit reduced digoxin bioavailability. Metabolomic profiling can capture the functional output of both host and microbial metabolism, providing a phenotypic readout that integrates genetic and environmental factors.

Epigenetic modifications, including DNA methylation and histone modifications, regulate gene expression without altering the DNA sequence. Age-related changes in CYP450 gene methylation may contribute to the well-documented decline in drug metabolism with aging. Environmental exposures, including smoking, diet, and concurrent medications, can alter epigenetic marks and modulate drug response in ways that are not predictable from genotype alone. In Figure 4, we summarized the precision pharmacy implementation framework.

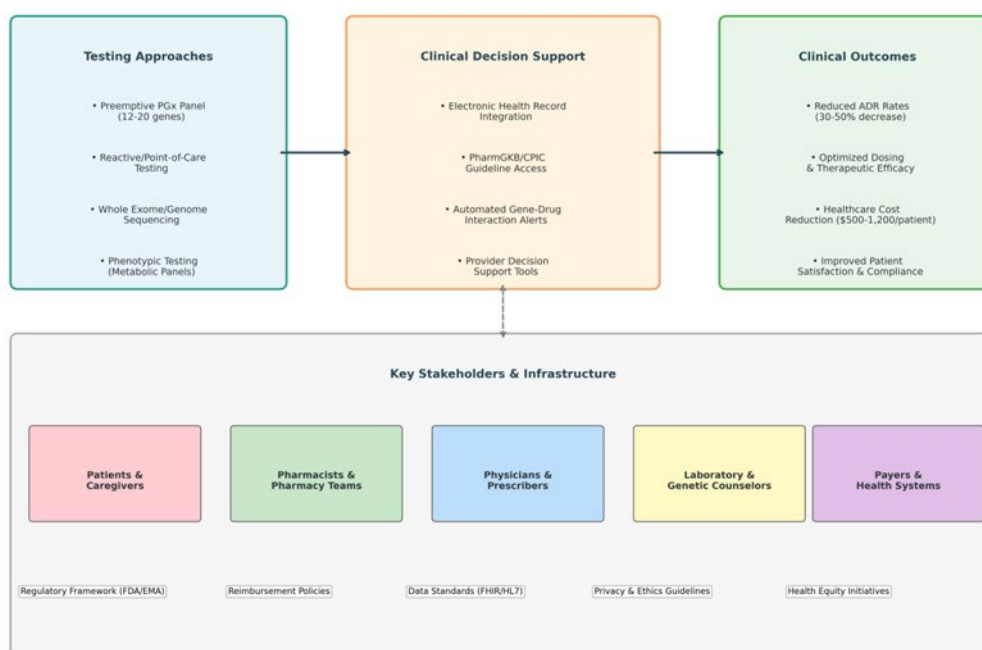


Figure 4. Precision pharmacy implementation framework. The framework integrates testing approaches, clinical decision support systems, and stakeholder engagement to achieve optimal clinical outcomes. Infrastructure components, including regulatory frameworks, reimbursement policies, and data standards, are critical enabling factors. Source: Authors, 2026.

6. Translational Advances in Pharmacogenomics

The field of pharmacogenomics is undergoing rapid transformation driven by technological innovations in data science, genomics, and implementation science. Artificial intelligence and machine learning approaches are increasingly being applied to pharmacogenomic prediction; polygenic risk scores are expanding the scope of genomic prediction beyond single-gene effects, and implementation science research is generating evidence on optimal strategies for clinical adoption.

6.1 Artificial intelligence and machine learning

Machine learning (ML) algorithms offer the potential to integrate pharmacogenomic data with clinical, demographic, and environmental variables to generate more accurate predictions of drug response than traditional models. Deep learning approaches, including neural networks and ensemble methods, can capture complex, non-linear interactions between genetic variants and clinical factors that are not readily modeled using linear regression (Lorenzini et al., 2024).

Several studies have demonstrated the potential of ML-enhanced pharmacogenomic prediction. Deep learning models for warfarin dose prediction have shown improved accuracy compared to the IWPC pharmacogenetic algorithm, particularly in underrepresented populations. Random forest and gradient boosting approaches for antidepressant response prediction have incorporated both pharmacogenomic and clinical variables to achieve prediction accuracies exceeding 70%. However, the clinical utility of ML-enhanced pharmacogenomic models remains to be established through prospective validation studies.

Natural language processing (NLP) techniques are being applied to extract pharmacogenomic information from unstructured clinical narratives, enabling the identification of ADR phenotypes and medication outcomes from electronic health records. These approaches facilitate the generation of real-world evidence for pharmacogenomic associations and the surveillance of gene-drug interaction outcomes in clinical practice.

Generative AI models, including large language models (LLMs), are being explored for pharmacogenomic education and clinical decision support. LLMs trained on pharmacogenomic literature can provide contextualized explanations of gene-drug interactions and guideline recommendations, potentially addressing

provider knowledge gaps and supporting shared decision-making with patients. However, concerns about accuracy, hallucination, and liability must be addressed before clinical deployment (Altman, 2023).

6.2 Polygenic risk scores in pharmacogenomics

While current pharmacogenomic practice focuses primarily on single-gene effects with large effect sizes, most drug response traits are polygenic, involving numerous variants of small individual effect. Polygenic risk scores (PRS), which aggregate the effects of many genetic variants across the genome, offer the potential to capture a greater proportion of genetic variance in drug response and improve prediction accuracy (Torkamani et al., 2018).

PRS approaches have shown particular promise for predicting warfarin dose requirements, antidepressant response, and statin efficacy. For warfarin, PRS incorporating thousands of variants across multiple pharmacokinetic and pharmacodynamic genes has explained up to 60% of dose variance, compared to 40-50% for candidate gene approaches. In psychiatry, polygenic scores for major depressive disorder and schizophrenia have been associated with antidepressant and antipsychotic response, respectively, though effect sizes remain modest.

Challenges for PRS implementation include the need for large, diverse training datasets; the limited transferability of PRS across populations; and the requirement for advanced bioinformatics infrastructure. Current PRS are predominantly derived from European-ancestry GWAS, resulting in reduced prediction accuracy in non-European populations. The transferability gap represents a critical barrier to equitable implementation that is being addressed through the inclusion of diverse populations in genomic studies and the development of population-specific PRS models.

6.3 Real-world evidence and implementation science

Implementation science, the study of methods to promote the systematic uptake of research findings into routine practice, has become increasingly important in pharmacogenomics. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework and the Consolidated Framework for Implementation Research (CFIR) have been applied to evaluate pharmacogenomic implementation programs and identify determinants of successful adoption (Roberts et al., 2017).

Real-world evidence (RWE) generated from EHR data, claims databases, and patient registries is complementing traditional RCT evidence for pharmacogenomic implementation. The FDA's Real-World Evidence program has established frameworks for using RWE to support regulatory decisions, including the evaluation of pharmacogenomic biomarkers. Large-scale observational studies leveraging biobanks linked to EHR data, such as the UK Biobank and the Million Veteran Program, have enabled the discovery and validation of pharmacogenomic associations in populations of unprecedented size.

Pharmacogenomic implementation research has identified several critical success factors: executive leadership support and institutional commitment; interdisciplinary implementation teams including pharmacists, genetic counselors, informaticists, and clinicians; systematic provider education programs; patient engagement and education strategies; and iterative quality improvement processes. Programs that have addressed these factors have generally achieved higher rates of provider adoption and better clinical outcomes. In Figure 5, we analyze artificial intelligence and multi-omics in pharmacogenomics.

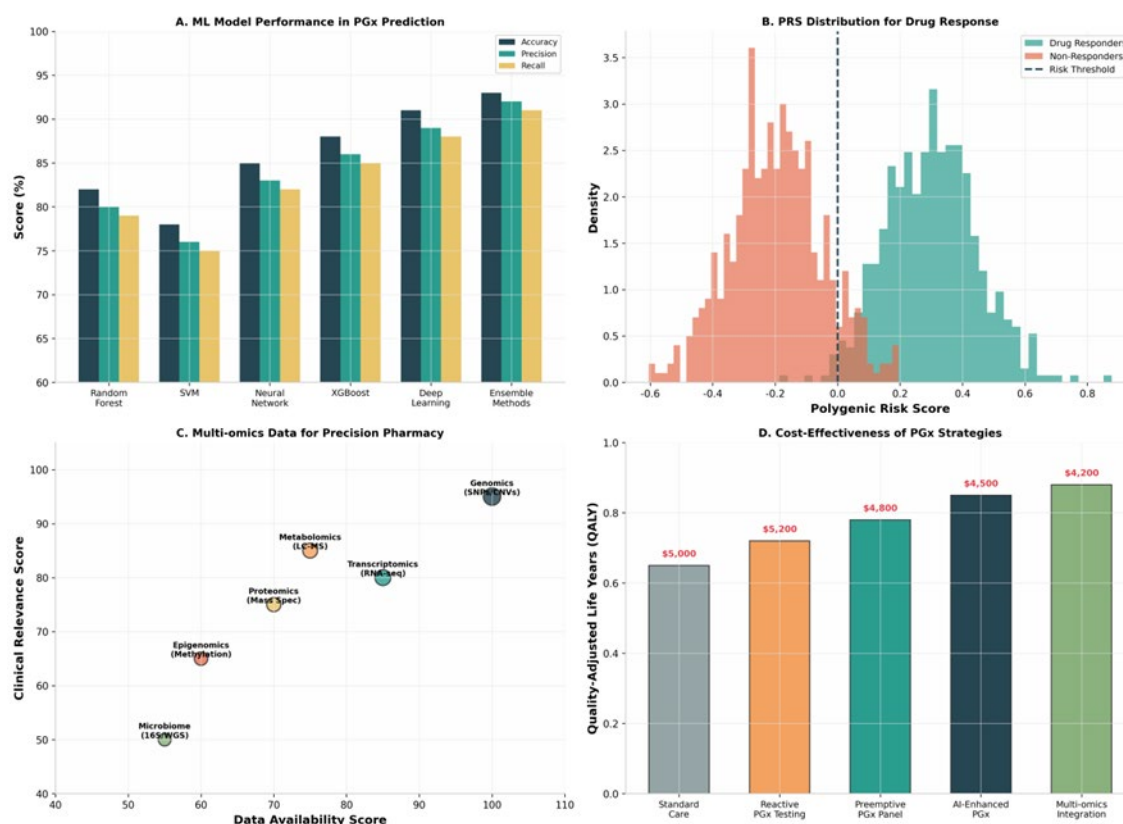


Figure 5. Artificial intelligence and multi-omics in pharmacogenomics. (A) Performance comparison of machine learning models for pharmacogenomic prediction. (B) Polygenic risk score distributions for drug responders and non-responders. (C) Multi-omics data integration landscape showing data availability versus clinical relevance. (D) Cost-effectiveness analysis of pharmacogenomic implementation strategies. Source: Authors, 2026.

7. Challenges and Barriers to Implementation

Despite compelling scientific evidence and growing clinical experience, the widespread implementation of pharmacogenomics faces significant challenges that span economic, regulatory, educational, and equity domains. Addressing these challenges requires coordinated efforts from stakeholders across the healthcare ecosystem, including policymakers, payers, healthcare systems, professional organizations, and patient advocacy groups.

7.1 Economic and reimbursement challenges

The economic landscape for pharmacogenomic testing remains complex and fragmented. Testing costs have declined substantially with advances in genotyping technology, with pharmacogenomic panels now available for \$100-300. However, reimbursement policies vary widely across payers and healthcare systems. In the United States, Medicare coverage for pharmacogenomic testing is limited and often requires prior authorization, while private payer policies are heterogeneous. The lack of standardized Current Procedural Terminology (CPT) codes for pharmacogenomic panels complicates billing and reimbursement (Hresko; Haga, 2019).

Cost-effectiveness analyses of pharmacogenomic testing have generally yielded favorable results for high-actionability gene-drug pairs, with incremental cost-effectiveness ratios below \$50,000 per quality-adjusted life year (QALY) for many applications. However, economic evaluations are highly sensitive to assumptions about testing costs, ADR rates, and the magnitude of clinical benefit. The preemptive testing model, in which results are generated before they are clinically needed, introduces additional economic complexity, as the value of testing depends on the probability that patients will be prescribed actionable medications during the period in which results remain valid.

Value-based payment models may facilitate pharmacogenomic adoption by aligning financial incentives with

patient outcomes. Accountable care organizations and bundled payment programs that bear financial risk for ADRs and therapeutic failures have stronger incentives to invest in pharmacogenomic testing. The integration of pharmacogenomics into quality metrics and pay-for-performance programs could further drive adoption.

7.2 Regulatory and ethical considerations

The regulatory framework for pharmacogenomic testing involves multiple agencies and evolving standards. In the United States, the FDA regulates pharmacogenomic tests as in vitro diagnostics (IVDs), with the level of oversight depending on test complexity and risk classification. The FDA's Table of Pharmacogenetic Associations provides a curated list of gene-drug relationships with varying levels of regulatory evidence, but does not constitute formal guideline recommendations. The Clinical Laboratory Improvement Amendments (CLIA) program sets quality standards for laboratory testing, including pharmacogenomic assays (Pratt et al., 2019).

Ethical considerations in pharmacogenomics include issues related to informed consent, incidental findings, data privacy, and genetic discrimination. Preemptive pharmacogenomic testing raises questions about the appropriate scope of consent, particularly when testing is performed in pediatric populations or when results may have implications for family members. The return of incidental or secondary pharmacogenomic findings, while generally considered less ethically complex than secondary findings from whole exome or genome sequencing, requires clear policies and patient communication strategies.

The Genetic Information Nondiscrimination Act (GINA) prohibits health insurers and employers from using genetic information for discriminatory purposes in the United States, but does not extend to life insurance, disability insurance, or long-term care insurance. Similar protections vary across countries, creating uncertainty about the long-term privacy of pharmacogenomic data. The increasing integration of genetic data with digital health platforms and wearable devices introduces additional privacy considerations.

7.3 Healthcare system integration

The successful integration of pharmacogenomics into healthcare systems requires coordinated changes across multiple dimensions, including clinical workflows, information systems, provider education, and quality assurance. Many healthcare systems lack the infrastructure to support pharmacogenomic testing, result interpretation, and clinical decision support. The fragmented nature of healthcare delivery in many countries complicates the tracking and application of pharmacogenomic results across care transitions.

Provider education represents a critical but often overlooked barrier to implementation. Surveys consistently demonstrate limited pharmacogenomic knowledge among prescribers, particularly regarding the clinical interpretation of test results and the application of guideline recommendations. Educational interventions, including didactic sessions, case-based learning, and clinical decision support, have been shown to improve provider knowledge and confidence, but the durability of these effects and their impact on prescribing behavior require further study (Vo et al., 2023).

Pharmacist-led pharmacogenomic services have emerged as a promising model for addressing provider knowledge gaps and facilitating implementation. Clinical pharmacists with specialized training in pharmacogenomics can provide direct patient care services, including test ordering, result interpretation, and therapeutic recommendations. The American College of Clinical Pharmacy and other professional organizations have developed certification programs for pharmacogenomics specialists, and pharmacist scope of practice regulations in many jurisdictions have been expanded to include pharmacogenomic clinical services.

7.4 Diversity, equity, and population genomics

Perhaps the most significant challenge facing pharmacogenomics is the lack of diversity in genomic research and its implications for health equity. The vast majority of pharmacogenomic discovery studies have been conducted in populations of European ancestry, resulting in allele frequency databases and clinical guidelines that may not be directly applicable to diverse global populations. This disparity has profound implications for the precision and equity of pharmacogenomic predictions across racial and ethnic groups (Martin et al., 2019).

Allele frequency differences across populations can lead to substantial variation in pharmacogenomic test yield and clinical actionability. For example, CYP2D6 ultra-rapid metabolizer duplications occur in 1-2% of Europeans but 10-30% of North Africans and Middle Eastern populations. CYP2C19 loss-of-function alleles are

present in 12-20% of Europeans but 50-65% of East Asians. *SLCO1B1**5 is more common in East Asians than in Europeans. These differences necessitate a population-specific approach to pharmacogenomic panel design, allele selection, and clinical decision support.

Several initiatives have been launched to address the diversity gap in pharmacogenomics. The NIH INCLUDE (Investigation of Co-occurring conditions across the Lifespan to Understand Down syndrome) project has generated pharmacogenomic data from underrepresented populations. The Human Heredity and Health in Africa (H3Africa) consortium has characterized pharmacogenetic variation across African populations. The Pharmacogenomics for Every Nation Initiative (PGENI) has worked with low- and middle-income countries to develop population-specific pharmacogenomic strategies. Despite these efforts, significant gaps remain, and achieving equitable pharmacogenomic healthcare will require sustained investment in diverse genomic research (Landry et al., 2018).

8. Future Perspectives

The field of pharmacogenomics stands at an inflection point, with scientific advances, technological innovations, and evolving healthcare needs converging to create both unprecedented opportunities and complex challenges (Qin et al., 2024; Wang et al., 2026). Looking ahead, several developments are likely to shape the trajectory of precision pharmacy over the coming decade.

8.1 Technological advances

Long-read sequencing technologies, including PacBio and Oxford Nanopore platforms, promise to overcome critical limitations of short-read sequencing for pharmacogenomic analysis. *CYP2D6*, in particular, has been challenging to genotype using short-read approaches due to its high sequence homology with pseudogenes and complex structural variation. Long-read sequencing enables complete haplotype resolution and accurate characterization of gene duplications and hybrid alleles, potentially improving genotype accuracy for this critical pharmacogene (Qin et al., 2024).

CRISPR-based functional genomics approaches, including base editing and prime editing, offer new tools for validating pharmacogenomic associations and characterizing variant effects. High-throughput functional assays, in which thousands of variants are introduced into cellular models and their effects on drug response are quantified, are accelerating the transition from variant identification to functional characterization. These approaches may ultimately enable the classification of variants of uncertain significance (VUS) that currently limit the clinical utility of pharmacogenomic testing.

Pharmacogenomic digital twins, computational models that integrate multi-scale biological data to simulate individual drug response, represent an emerging paradigm for precision pharmacy (Muhammad et al., 2026). These models incorporate pharmacogenomic, physiological, and environmental data to generate dynamic predictions of drug exposure and response, potentially enabling *in silico* clinical trials and personalized dosing optimization. While still in early development, digital twin approaches hold promise for addressing the complexity of drug response beyond what is achievable with genotype-based algorithms alone.

8.2 Policy and regulatory landscape

The policy environment for pharmacogenomics is evolving rapidly, with implications for reimbursement, regulation, and clinical adoption. The FDA's Precision Medicine Initiative and the European Medicines Agency's (EMA) pharmacogenomic biomarker qualification program are establishing regulatory pathways for the clinical use of pharmacogenomic tests. The Centers for Medicare and Medicaid Services (CMS) National Coverage Determination process has the potential to standardize Medicare reimbursement for pharmacogenomic testing, though progress has been slow.

International harmonization of pharmacogenomic guidelines and regulatory standards remains an important goal. Differences between CPIC and DPWG recommendations, while generally minor, can create confusion for clinicians and complicate the development of global clinical decision support tools (Jia et al., 2026). The International Union of Basic and Clinical Pharmacology (IUPHAR) Pharmacogenomics Knowledge Base and other international initiatives are working toward greater harmonization of pharmacogenomic standards.

The integration of pharmacogenomics into undergraduate medical and pharmacy curricula is essential for preparing the next generation of healthcare providers. The Global Genomics and Health Alliance (GA4GH) and

the Pharmacogenomics Global Research Network have developed educational resources and competency frameworks for pharmacogenomics education. However, significant gaps remain, and many practicing clinicians have received minimal pharmacogenomics training.

8.3 Global health applications

The application of pharmacogenomics to global health challenges represents an important frontier for the field. Infectious disease pharmacogenomics, including the genomics of antiretroviral therapy, antimalarial drugs, and anti-tuberculosis medications, has direct relevance to disease burden in low- and middle-income countries. Pharmacogenomic optimization of these therapies could improve treatment outcomes and reduce the emergence of drug resistance in resource-limited settings (Rodrigues et al., 2023).

The development of affordable, point-of-care pharmacogenomic testing platforms could democratize access to precision pharmacy services. Isothermal amplification technologies, microfluidic devices, and smartphone-based readout systems are being developed for pharmacogenetic analysis in settings without access to centralized laboratory infrastructure. The WHO Essential Medicines List includes pharmacogenomic biomarkers for several medications, providing a framework for prioritizing pharmacogenomic implementation in resource-limited settings. In Figure 6, we analyze the Global landscape and challenges in pharmacogenomics implementation. And in Figure 7, we have summarized the translational pipeline and future directions in precision pharmacy.

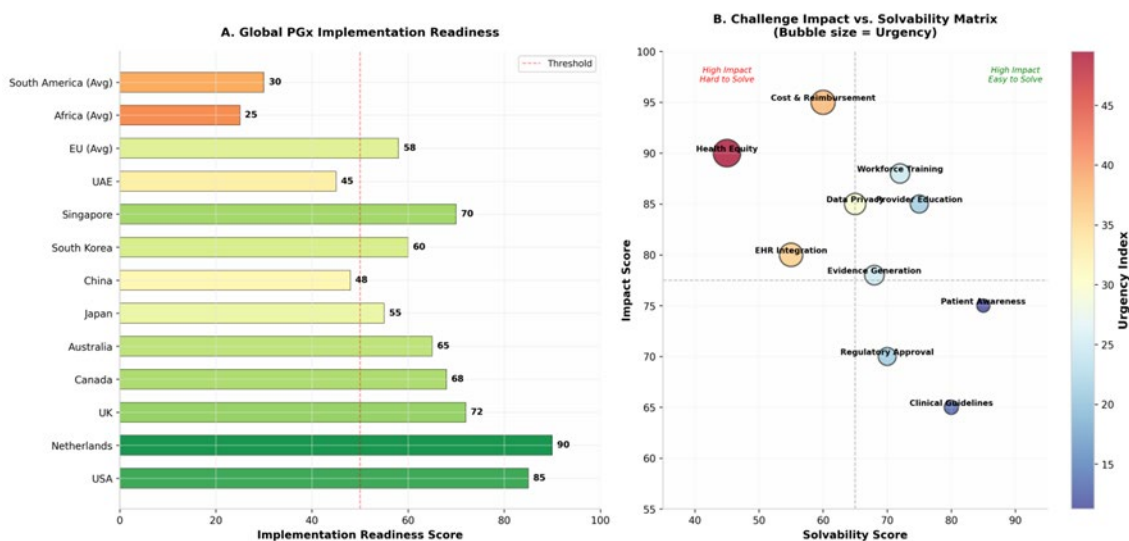


Figure 6. Global landscape and challenges in pharmacogenomics implementation. (A) Implementation readiness scores across countries and regions. (B) Challenge impact versus solvability matrix, with bubble size indicating urgency. Challenges in the upper left quadrant (high impact, low solvability) require prioritized attention. Source: Authors, 2026.

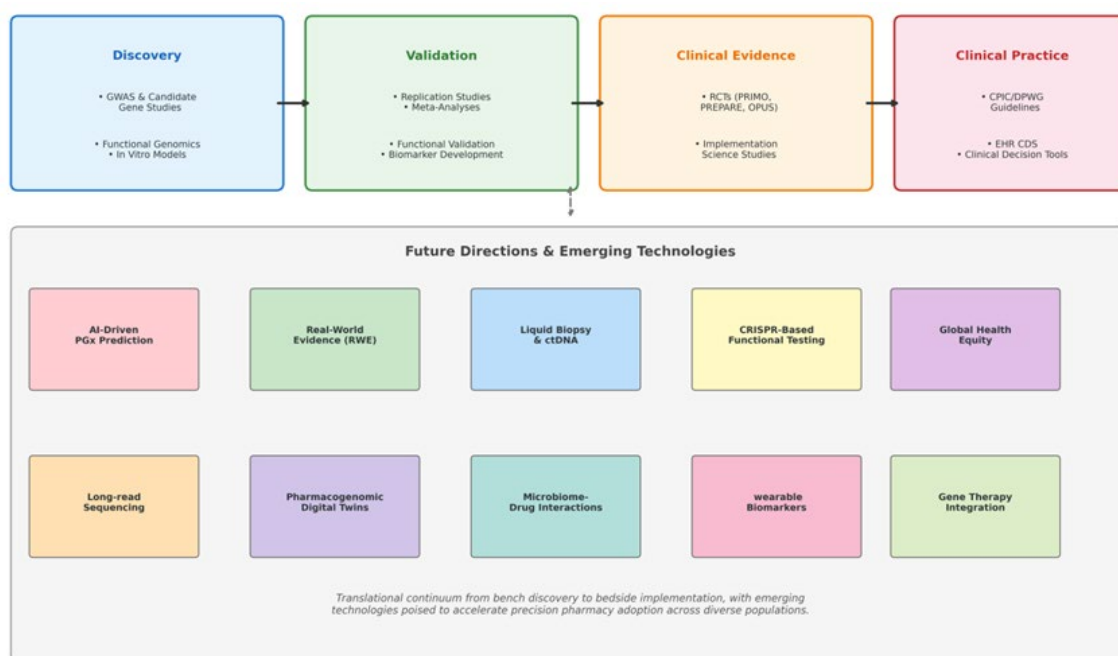


Figure 7. Translational pipeline and future directions in precision pharmacy. The translational continuum spans from discovery research through validation, clinical evidence generation, and clinical practice implementation. Emerging technologies, including AI-driven prediction, real-world evidence generation, liquid biopsy, CRISPR-based functional testing, and global health equity initiatives, represent critical future directions. Source: Authors, 2026.

9. Conclusions

Pharmacogenomics has transitioned from a research discipline to a clinical reality, with robust evidence supporting the implementation of genotype-guided prescribing for multiple gene-drug pairs. The mechanisms by which genetic variation influences drug response are increasingly well-characterized, and international guideline consortia have developed evidence-based recommendations for clinical action. Major implementation programs have demonstrated the feasibility and clinical utility of preemptive pharmacogenomic testing across diverse healthcare settings.

However, significant challenges remain in achieving equitable access to pharmacogenomic services. The diversity gap in genomic research limits the applicability of current guidelines to non-European populations, and economic, regulatory, and educational barriers impede widespread adoption. Addressing these challenges will require sustained investment in diverse genomic research, policy reforms to support reimbursement and regulation, and comprehensive provider education programs.

Emerging technologies, including artificial intelligence, polygenic risk scores, long-read sequencing, and multi-omics integration, offer opportunities to enhance the precision and scope of pharmacogenomic prediction. The integration of pharmacogenomics into routine clinical practice, supported by robust clinical decision support systems and interdisciplinary care teams, represents the next frontier for precision pharmacy.

As the field continues to evolve, the ultimate measure of success will be the extent to which pharmacogenomics improves patient outcomes, reduces healthcare costs, and advances health equity across diverse populations. Achieving this vision will require the continued collaboration of researchers, clinicians, policymakers, and patients in building a precision pharmacy ecosystem that delivers on the promise of individualized drug therapy for all.

The convergence of technological innovation, growing clinical evidence, and evolving healthcare paradigms positions pharmacogenomics as a cornerstone of 21st-century medicine. Healthcare systems that invest in pharmacogenomic infrastructure, education, and implementation will be best positioned to realize the benefits of precision pharmacy for their patients and communities.

10. Authors' Contributions

Hao Sun: conceptualization, methodology, investigation, data curation, writing – original draft. Zijun Qiao: investigation, formal analysis, data curation, visualization. Jinze Yu: investigation, validation, resources. Gaoyang Guo: software, formal analysis, visualization. Liangyu Li: supervision, project administration, funding acquisition, writing – review & editing.

11. Conflicts of Interest

No conflicts of interest.

12. Ethics Approval

Not applicable.

13. Artificial Intelligence Statement: Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

Artificial intelligence (AI) was used solely to assist with language editing, including grammatical corrections and improvements to the clarity, readability, and overall writing of the manuscript. AI was not used to generate, analyze, interpret, or modify the scientific content, research data, results, figures, tables, or conclusions. All scientific content was conceived, reviewed, verified, and approved by the authors, who assume full responsibility for the accuracy, integrity, and originality of the manuscript.

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