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ROLE OF PHARMACOGENOMICS IN INDIVIDUALIZED PHARMACOTHERAPY

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Abstract

Pharmacogenomics (PGx) aims to use inherited genetic variation to improve the selection and dosing of medicines. Its clinical relevance is strongest when genetic information is combined with conventional determinants of drug response, including age, organ function, interacting medicines, disease severity and treatment goals. This structured review evaluates the role of PGx in individualized pharmacotherapy, emphasizing actionable gene–drug pairs, evidence from implementation studies, guideline-based prescribing, and practical barriers to routine use. International evidence was synthesized from peer-reviewed clinical trials, implementation studies, CPIC guidelines, and major reviews. The findings show that PGx is most mature for drugs affected by polymorphic drug-metabolizing enzymes, transporters, immune-risk alleles, and selected pharmacodynamic pathways. Examples include CYP2C19-guided antiplatelet therapy, CYP2D6/CYP2C19-guided antidepressant prescribing, TPMT/NUDT15-guided thiopurine dosing, SLCO1B1/ABCG2/CYP2C9-guided statin therapy, and multigene approaches for preventing adverse drug reactions. The PREPARE implementation study demonstrated that a 12-gene panel can reduce clinically relevant adverse drug reactions when prescribing is adjusted according to established recommendations. Nevertheless, clinical utility depends on test quality, population representation, guideline concordance, electronic decision support, reimbursement, and clinician education. PGx should therefore be viewed as a component of precision pharmacotherapy rather than an isolated genetic test. Future progress will depend on pre-emptive panel testing, interoperable electronic health records, better evidence in diverse populations, and integration of genomic data with therapeutic drug monitoring and other clinical biomarkers.

Keywords: pharmacogenomics; pharmacogenetics; precision medicine; individualized pharmacotherapy; drug–gene interaction; clinical decision support; adverse drug reactions.

1. INTRODUCTION

Interindividual variability in medicine response remains a major challenge in clinical pharmacology. Patients receiving the same medicine at the same dose may experience therapeutic success, inadequate efficacy, or severe toxicity. Drug response is shaped by many factors, including age, body composition, kidney and liver function, adherence, diet,

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comorbidities, drug–drug interactions and genetic variation. Pharmacogenomics investigates how inherited differences across the genome influence pharmacokinetics, pharmacodynamics and immune-mediated adverse reactions, thereby offering a biologically grounded route to more individualized prescribing (1,2).

The clinical relevance of PGx has moved beyond proof-of-concept associations toward implementation frameworks that translate genotype into phenotype and then into a prescribing recommendation. The Clinical Pharmacogenetics Implementation Consortium (CPIC) develops freely available gene–drug guidelines for situations in which genetic results are already available, while the Dutch Pharmacogenetics Working Group (DPWG) and other national groups provide complementary recommendations (1,8). These resources are increasingly linked to electronic health records and clinical decision support systems so that genomic information can be reused throughout a patient's lifetime rather than interpreted as a one-time laboratory result (9,12).

A central advantage of PGx is the possibility of anticipating atypical exposure or toxicity before treatment begins. Loss-of-function alleles in CYP2C19 can reduce clopidogrel bioactivation, TPMT and NUDT15 deficiency can markedly increase thiopurine myelosuppression, and reduced SLCO1B1 transport can increase systemic statin exposure and the risk of musculoskeletal adverse effects (3,5,6). Conversely, ultra-rapid metabolism can lower exposure to certain antidepressants and analgesics. Pharmacogenomic effects may therefore alter drug choice, starting dose, titration strategy, monitoring intensity, or the threshold for choosing a therapeutic alternative.

The objective of this article is to evaluate the role of pharmacogenomics in individualized pharmacotherapy using an IMRAD structure. Particular attention is given to clinically actionable gene–drug pairs, multigene pre-emptive testing, evidence for improved safety, and the practical steps required to convert a laboratory genotype into a safe therapeutic decision.

2. MATERIALS AND METHODS

A structured narrative review approach was used to synthesize current evidence on pharmacogenomics-guided pharmacotherapy. Sources were selected from peer-reviewed clinical pharmacology, pharmacogenomics and precision-medicine literature, together with guideline publications and implementation studies. Priority was given to CPIC guidance, randomized or prospective clinical evidence, systematic or implementation-focused reviews, and recent literature describing health-system integration.

The synthesis focused on four analytical domains: (i) mechanisms by which inherited variation alters drug response; (ii) clinically actionable gene–drug pairs; (iii) evidence for patient-level benefit and safety; and (iv) implementation requirements including testing strategy, phenotype translation, electronic clinical decision support, education and equity. Studies were not pooled statistically because the interventions, drug classes, genetic variants and clinical outcomes were heterogeneous. Results are therefore presented as a comparative qualitative synthesis rather than a meta-analysis.

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For practical interpretation, gene–drug pairs were classified by their dominant mechanism: pharmacokinetic effects on metabolism or transport, pharmacodynamic effects on drug targets, or immune-mediated risk. The review also distinguishes reactive testing, ordered after a specific medicine is being considered, from pre-emptive panel testing, in which multiple pharmacogenes are genotyped before future prescribing needs arise.

3. RESULTS

3.1. Pharmacogenomic determinants of drug response

The most established PGx associations involve genes encoding drug-metabolizing enzymes and transporters. Cytochrome P450 enzymes such as CYP2D6, CYP2C19 and CYP2C9 can vary from little or no functional activity to increased activity, leading to clinically important differences in exposure. These effects are particularly relevant when a drug has a narrow therapeutic index, when it requires metabolic activation, or when alternative therapies are available. Transporter genes such as SLCO1B1 and ABCG2 can similarly affect intracellular and systemic drug concentrations (3–5).

Pharmacodynamic and immune mechanisms are also important. Certain HLA alleles can predict serious hypersensitivity reactions, while variants in drug targets or signaling pathways may modify efficacy or toxicity. However, not every statistically significant association is clinically actionable. A useful PGx result requires robust phenotype translation, reproducible clinical evidence and a therapeutic action that improves the benefit–risk balance. This distinction explains why some genes are recommended for routine prescribing decisions while others remain primarily research biomarkers (4,8).

Table 1. Selected clinically actionable pharmacogenomic examples in individualized pharmacotherapy

Gene(s)	Drug / class	Main pharmacologic effect	Individualized prescribing implication
CYP2C19	Clopidogrel	Reduced bioactivation in intermediate/poor metabolizers	Consider an alternative P2Y12 inhibitor where guideline indications support it (3).
CYP2D6 / CYP2C19 / CYP2B6	Serotonin reuptake inhibitors	Altered metabolism and exposure	Use phenotype-informed drug or dose recommendations for selected antidepressants (4).
TPMT / NUDT15	Thiopurines	Reduced inactivation of active thiopurine metabolites	Reduce starting dose or use alternative strategy in reduced-function phenotypes; close monitoring remains essential (6).

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Gene(s)	Drug / class	Main pharmacologic effect	Individualized prescribing implication
SLCO1B1 / ABCG2 / CYP2C9	Statins	Altered hepatic transport or metabolism	Adjust statin choice or dose to lower risk of statin-associated musculoskeletal symptoms (5).
CYP2C9 / VKORC1 / CYP4F2	Warfarin	Altered clearance and pharmacodynamic sensitivity	Use validated genotype-informed dosing algorithms together with clinical variables and INR monitoring (7).
HLA risk alleles	Selected high-risk medicines	Immune-mediated hypersensitivity	Avoid implicated medicine when a validated high-risk genotype is present and guideline criteria are met.

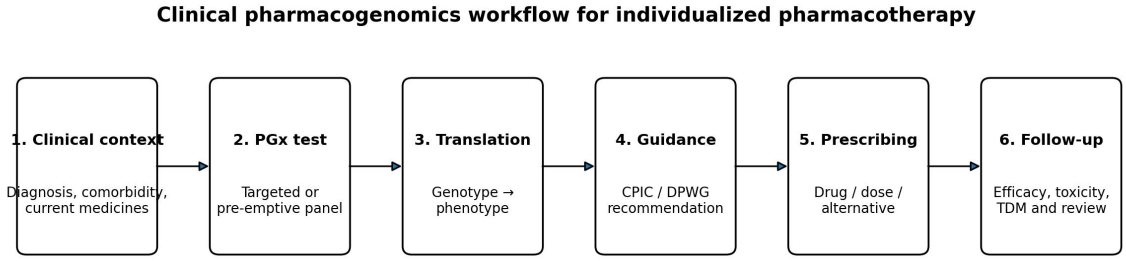
3.2. Evidence from multigene implementation

Single gene–drug pairs demonstrate biological validity, but the long-term value of PGx is greatest when results can inform multiple future prescriptions. The PREPARE study evaluated a 12-gene panel across hospitals, community health centers and pharmacies in seven European countries. Adults starting medicines covered by DPWG recommendations were managed either with genotype-guided prescribing or usual care. The study provided prospective evidence that panel-based pharmacogenetic guidance can reduce clinically relevant adverse drug reactions, supporting a shift from purely reactive testing toward pre-emptive strategies (2).

Pre-emptive testing has a different value proposition from one-drug testing. A panel result can be stored in the electronic health record and repeatedly reused when new medicines are prescribed. This makes PGx particularly relevant for patients with multimorbidity and polypharmacy, in whom several actionable gene–drug interactions may become clinically relevant over time. However, the benefit is realized only if the laboratory output is converted into standardized phenotype labels and embedded into the prescribing workflow (1,9,12).

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Figure 1. Clinical pharmacogenomics workflow for individualized pharmacotherapy



3.3. Reactive versus pre-emptive testing

Reactive testing is often easier to justify because the clinical question is immediate: a specific medicine is being considered, and a known gene may alter its safety or efficacy. The disadvantages are turnaround time and the risk that treatment must start before the result is available. Pre-emptive panel testing solves the timing problem by generating reusable information in advance, but it requires greater investment in laboratory systems, data storage, clinical interpretation and governance (9–12).

The choice between targeted and panel testing should therefore depend on clinical setting, population, medication exposure, turnaround requirements and infrastructure. High-value settings include cardiology, psychiatry, oncology, transplant medicine, pain management and primary care populations with frequent medication changes. In all settings, PGx should supplement rather than replace standard clinical assessment, therapeutic drug monitoring, laboratory monitoring and shared decision-making.

Table 2. Practical comparison of pharmacogenomic testing strategies

Strategy	Strengths	Limitations	Best-fit use
Reactive single-gene testing	Directly linked to an immediate prescribing decision; lower initial scope	Turnaround may delay therapy; repeated testing can fragment care	High-risk gene–drug pairs when treatment is imminent
Reactive multigene panel	Broader information from one sample	Some results may not be immediately useful; interpretation is more complex	Patients with polypharmacy or multiple plausible therapies

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Strategy	Strengths	Limitations	Best-fit use
Pre-emptive panel	Results available before future prescribing; reusable across encounters	Upfront cost, data governance, EHR integration and education required	Health systems with mature decision support and high lifetime medication exposure
Embedded clinical decision support	Delivers recommendation at the point of prescribing	Alert fatigue and poor rule design can reduce effectiveness	Large systems seeking scalable implementation (12)

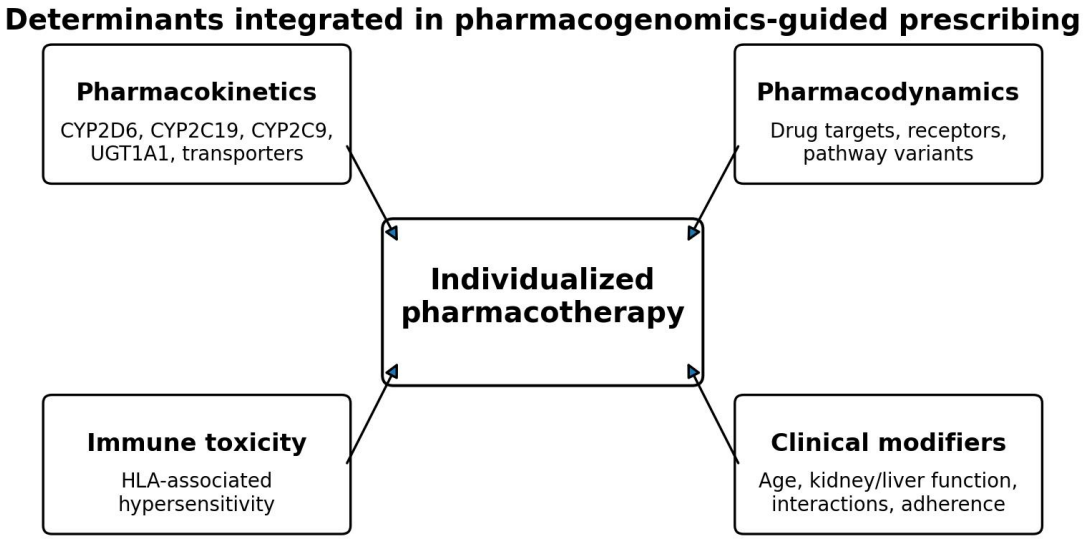
3.4. Pharmacogenomics as part of multimodal precision pharmacotherapy

Genotype alone rarely explains all variability in drug response. A CYP phenotype may be modified by inhibitors or inducers, a phenomenon sometimes called phenoconversion, while kidney or liver impairment can alter exposure independently of genotype. For narrow-therapeutic-index drugs, PGx is therefore strongest when combined with clinical variables, concentration monitoring and response assessment. Warfarin illustrates this principle: genetic information can improve initial dose estimation, but INR monitoring remains indispensable throughout treatment (7).

Similarly, antidepressant guidance uses CYP2D6, CYP2C19 and CYP2B6 for selected drugs, but disease severity, prior response, co-medications and tolerability remain central to the final decision. CPIC does not support routine prescribing decisions based on SLC6A4 or HTR2A because evidence is insufficient for clinically reliable action, underscoring the difference between biological plausibility and actionable pharmacogenomics (4).

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Figure 2. Determinants integrated in pharmacogenomics-guided prescribing



4. DISCUSSION

The evidence reviewed indicates that pharmacogenomics has progressed from an exploratory research field to a practical component of individualized pharmacotherapy. The strongest applications share several features: a well-characterized functional variant, a reproducible effect on exposure or toxicity, an accepted phenotype-translation system, and a clear prescribing action. CPIC's continuing expansion and international uptake reflect this maturation, but guideline availability does not automatically guarantee clinical implementation (1,10).

Clinical benefit is especially plausible when PGx prevents serious toxicity or treatment failure. The PREPARE trial is important because it tested a panel strategy in routine-care settings rather than evaluating a single gene–drug pair in isolation (2). At the same time, commentators have noted methodological and interpretive limitations, reminding clinicians that the magnitude of benefit may vary by population, medicine, clinical endpoint and local prescribing practice. PGx should therefore be introduced with outcome monitoring rather than treated as universally beneficial for every prescription.

Implementation remains limited by non-genetic barriers. These include reimbursement, inconsistent availability of testing, laboratory standardization, provider confidence, result portability, interoperability and the design of clinical decision support. Recent reviews show that many historical barriers have decreased, while equity, evidence thresholds, education and EHR integration remain major priorities (10–14). If a pharmacogenomic result is buried in a laboratory report without a prescribing recommendation, its practical value is low. Conversely, a well-designed alert that appears only when a relevant medicine is ordered can transform a lifetime genomic result into a point-of-care clinical action (12).

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Population diversity is another critical issue. Allele frequencies and the distribution of functional variants differ across ancestral backgrounds, and some historical evidence bases overrepresent populations of European ancestry. This can reduce test sensitivity or generalizability when panels omit variants that are more frequent in other populations. Contemporary implementation must therefore avoid a narrow one-size-fits-all approach and should use assays validated for the populations being served (10,13,15). The 2025 CPIC thiopurine update illustrates the importance of considering TPMT and NUDT15 variation across world populations rather than assuming a single ancestry-specific risk model (6).

From a pharmacoeconomic perspective, value depends on how often actionable results are used, the severity and cost of avoidable adverse events, test price and whether results can be reused. A pre-emptive panel can become more cost-efficient when a patient encounters multiple relevant medicines over time. This favors integration into longitudinal records and suggests that PGx may have particular relevance for older adults, people with chronic disease and individuals receiving complex multidrug therapy.

Future individualized pharmacotherapy is likely to integrate genomics with therapeutic drug monitoring, renal and hepatic biomarkers, digital adherence data and computational dosing models. Such integration is more biologically realistic than attempting to predict outcome from genotype alone. The long-term goal is therefore not 'genetic prescribing' but precision pharmacotherapy in which genomic information is one durable layer of evidence combined with dynamic clinical data.

5. CONCLUSION

Pharmacogenomics can improve individualized pharmacotherapy by identifying inherited differences that alter drug metabolism, transport, immune toxicity and selected pharmacodynamic responses. Its most mature clinical applications include CYP2C19-guided antiplatelet therapy, CYP2D6/CYP2C19/CYP2B6-informed antidepressant use, TPMT/NUDT15-guided thiopurine dosing, SLCO1B1/ABCG2/CYP2C9-guided statin therapy and genotype-informed warfarin initiation. Evidence from multigene implementation studies supports the feasibility of pre-emptive testing and suggests that guideline-concordant prescribing can reduce clinically relevant adverse drug reactions. Nevertheless, PGx is not a substitute for clinical judgment, therapeutic monitoring or patient-centered care. Sustainable implementation requires validated testing, standardized genotype-to-phenotype translation, electronic decision support, clinician education, reimbursement, and better evidence across genetically diverse populations. When these elements are integrated, pharmacogenomics becomes a reusable clinical resource that can contribute meaningfully to safer, more effective and more precise pharmacotherapy.

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