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Pharmacogenomics and Personalized Drug Therapy: Advances in Genetic Variants, Drug Response Prediction, and Precision Medicine

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Abstract: ***The study of individual drug response due to genetic variation, known as Pharmacogenomics (PGx), has transitioned from a research concept to become a key component of precision medicine in the clinic. New advances in genetic research have led to the identification of variants of cytochrome P450 metabolising enzymes (such as CYP2D6, CYP2C19, CYP2C9) and drug transporters (SLCO1B1), and human leukocyte antigen (HLA) genes, which account for much of the inter-individual differences in efficacy and toxicity of commonly used drug classes including antiplatelets, anticoagulants, antidepressants, statins, and chemotherapeutic drugs. This review collates recent literature (2020-2025) on three interwoven themes: (i) clinically actionable genetic variants and guidance for their use in consortia, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC); (ii) the progression of drug response prediction, from rule-based algorithms through regression-based dosing models to novel machine learning and deep learning approaches incorporating multi-omics data; and (iii) the implementation of precision medicine, such as embedding clinical decision support in electronic health records (EHRs), establishing preemptive testing programmes, and the ongoing challenges of ancestral diversity, cost-effectiveness, and workforce education. We include a summary table of representative drug-gene pairs, a methodological comparison table, and an implementation efforts table, along with four figures visualising the PGx prescribing workflow, cytochrome P450 metabolizer phenotypes, an artificial intelligence approach to the prediction pipeline, and global disparities in pharmacogenomic representation. We believe the scientific and regulatory foundation for pharmacogenomic-informed prescribing is developing, but translating it into routine use worldwide remains an unfinished agenda that will require coordinated clinical, informatics, and policy action.***

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Keywords: ***Pharmacogenomics; Precision Medicine; Pharmacogenetic Variants; Cytochrome P450; Drug-Gene Interactions; Machine Learning; Personalized Drug Therapy***

Nomenclature:
CPIC: Clinical Pharmacogenetics Implementation Consortium
ML: Machine Learning
AI: Artificial Intelligence
DL: Deep Learning
CDS: Clinical Decision Support
DPWG: Dutch Pharmacogenetics Working Group
CYP: Cytochrome P450
SSRIs: Selective Serotonin Reuptake Inhibitors
HLA: Human Leukocyte Antigen
HER: Electronic Health Record

I. INTRODUCTION

One of the most intractable problems encountered in clinical pharmacotherapy is interindividual variability in drug efficacy and safety. In particular, inherited genetic differences in enzymes, transporters, and immune-recognition molecules involved in drug absorption, distribution, metabolism, excretion, and target engagement can explain much of this variation [1]. Pharmacogenomics (PGx), an integral part of the broader precision medicine movement, aims to customise prevention and treatment according to the individual's genome; it rests on genome-scale and targeted genotyping technologies to identify these variants and provide actionable prescribing guidance [2].

Over the last 20 years, it has advanced from candidate gene association studies to systematic, consortium-supported clinical guidelines. Today, the Clinical Pharmacogenetics Implementation Consortium (CPIC) alone publishes evidence-graded recommendations for 34 genes and 164 drugs, which are now effectively an international standard for converting the genome into prescription recommendations [3]. Genotype-informed dosing has been incorporated into routine use for a wide range of drugs, including antiplatelets, anticoagulants, antidepressants, statins, and cytotoxic chemotherapy, through parallel activities by the Dutch Pharmacogenetics Working Group and several national implementation programs [4,5].

At the same time, computational biology and Artificial Intelligence (AI) have begun to transform drug-response prediction. Classical PGx algorithms were single- or few-gene rule-based, while more modern PGx approaches increasingly leverage multi-omic data that incorporate genomic, transcriptomic, and clinical information and are modelled by machine

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learning (ML) and deep learning (DL) architectures that can model polygenic and nonlinear contributions to drug response, especially in oncology [6-10].

Yet implementation remains uneven, and scientific momentum is lacking. Persistent gaps include underrepresentation of non-European ancestries in discovery cohorts, inconsistent commercial test interpretation, limited clinical decision support (CDS) infrastructure outside specialised academic centres, and unresolved questions of cost-effectiveness and reimbursement [11-14]. This review aims to bring together the latest evidence (2020-2025) from three distinct areas of interest, clinically actionable genetic variants, methods of prediction of drug response and real-world precision medicine implementation, to provide an integrated, up-to-date resource to clinicians, pharmacists and translational researchers.

II. METHODOLOGY

This article is a narrative literature review, not a systematic review or meta-analysis; we did not register a protocol beforehand, and we did not formally pool effect estimates.

A. Search strategy

The search strategy used electronic databases such as PubMed/MEDLINE, Embase, Scopus, and Web of Science, and included English-language, peer-reviewed publications from January 2020 to the search date in 2025. Search terms combined, using Boolean operators, the concepts "pharmacogenomics," "pharmacogenetics," "drug-gene interaction," and "personalized/precision medicine" with gene- and drug-specific terms (e.g., CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP4F2, SLCO1B1, DPYD, HLA-B, TPMT, NUDT15), with prediction-methodology terms (e.g., "machine learning," "deep learning," "drug response prediction," "multi-omics"), and with implementation-related terms (e.g., "clinical decision support," "preemptive genotyping," "cost-effectiveness," "health equity"). We searched the published guideline repositories of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) and hand-searched the reference lists of retrieved reviews and guidelines to find additional eligible studies.

B. Eligibility criteria

Consortium guidelines, systematic and narrative reviews, cohort and registry studies, methodological/computational studies of clinically actionable pairs of genes and drugs and/or approaches to drug response prediction and real-world precision medicine implementation. We excluded case reports, non-peer-reviewed preprints, conference abstracts not available as full text, animal/preclinical studies, and studies not reporting human pharmacogenomics. We prioritised guideline updates, large observational cohorts, and publications since 2020, and included a small number of foundational earlier studies when they formed the main basis for the current guideline.

Titles and abstracts were screened for relevance to one of three pre-defined domains: (i) clinically actionable genetic variants and guideline-based management; (ii) methods for predicting drug response; and (iii) real-world implementation of precision medicine. We then assessed full texts for potentially eligible studies. We retrieved data on gene-drug pairs, genotype/phenotype, clinical evidence level, and implementation setting, and narratively and qualitatively integrated them by domain, presenting them in tables and figures in the summary rather than aggregating them quantitatively.

C. Limitations of Methodology

This is a narrative, not a systematic, review; therefore, we did not use formal risk-of-bias appraisal methods such as GRADE or ROBIS, and source selection still relies on investigator judgment. The review emphasises coverage of consortium guidelines, high-impact clinical studies, and recent methodological advances over exhaustive enumeration of each gene-drug association, and results should be viewed as an up-to-date, comprehensive, and integrated synthesis of the literature, not a systematic and complete list of all gene-drug associations.

III. GENETIC VARIANTS AFFECTING DRUG METABOLISM AND RESPONSE

A. Cytochrome P450 Enzymes and Metabolizer Phenotypes

The cytochrome P450 (CYP) superfamily is still the most clinically important pharmacogene family. CYP2D6 metabolises an estimated 15% of all prescribed drugs, and its highly polymorphic locus gives rise to different phenotypes (i.e., different enzyme activities), including poor, intermediate, normal, rapid, and ultrarapid metabolizer phenotypes, with dichotomous drug-exposure responses. CYP2D6 is highly polymorphic and gives rise to poor, intermediate, normal, rapid, and ultrarapid metabolizer phenotypes with divergent drug exposure and dichotomous responses. CPIC has developed new guidelines that correlate CYP2D6 (often in combination with adrenergic receptor genes) with beta-blocker dosing and with the selection and dosing of selective serotonin reuptake inhibitors (SSRIs), as well as CYP2C19, CYP2B6, SLC6A4, and HTR2A [15, 16]. A recent narrative review of psychiatric pharmacogenomics highlights the rapid clinical translation of these gene-drug combinations and the ongoing controversy over their effect sizes in genetically diverse psychiatric patients [17].

The CYP2C19 example illustrates the potential cardiovascular implications of a single well-characterised gene-drug interaction. In 2022, the CPIC update confirmed that carriers of the loss-of-function alleles (2, 3) have a significantly increased risk of stent thrombosis and recurrent ischemic events when receiving a typical clopidogrel dose following PCI [18]. Large observational cohorts have confirmed this signal: a 5-year Korean registry of drug-eluting stents revealed that loss-of-function carriers had significantly more atherothrombotic events during the first few months of therapy [19], and a British-South Asian cohort showed a significantly higher frequency of the CYP2C19 loss-of-function allele and an increased risk of recurrent myocardial infarction [20], indicating the population-specific consequences of not

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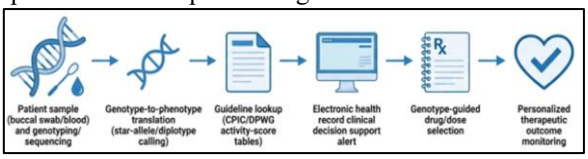
accounting for pharmacogenomic risk. Figure 1 presents the Pharmacogenomic-guided precision drug therapy, from sample collection to prescribing decision.



[Fig.1: Integrated Workflow of Pharmacogenomic-Guided Precision Drug Therapy, from Sample Collection to Prescribing Decision]

Sources: Conceptual synthesis based on the global implementation framework for precision-medicine pharmacogenomics adapted from references [1,2].

B. Vitamin K Antagonist Response, Transporters, and Fluoropyrimidine Toxicity

Combined genetic–clinical dosing algorithms have long been recognised as a paradigm of warfarin dosing. CYP2C9 (reduced-function alleles *2*3), the VKORC1 promoter, and CYP4F2 all affect the maintenance dose. A 2023 Iranian cohort study including these three loci, as well as clinical covariates, accounted for about 56% of dosing variability and performed better than previously published algorithms in that population, demonstrating the utility and population specificity of such models [21].

The SLCO1B1 hepatic uptake transporter also affects statin disposition. The 2022 CPIC guideline for SLCO1B1, ABCG2 and CYP2C9 documents the association between reduced-function SLCO1B1 alleles and higher systemic exposure to statins, and offers starting-dose recommendations for seven widely used statins [22]. In the field of oncology, DPYD variant screening before fluoropyrimidine chemotherapy has proven to be one of the most effective and impactful safety interventions in the province of British Columbia: A British Columbia program for prospective screening and dose reduction in carriers of DPYD variants has shown that this approach significantly reduced severe and potentially life-threatening toxicity; this preemptive screening program was expanded from a pilot to a province-wide service [23].

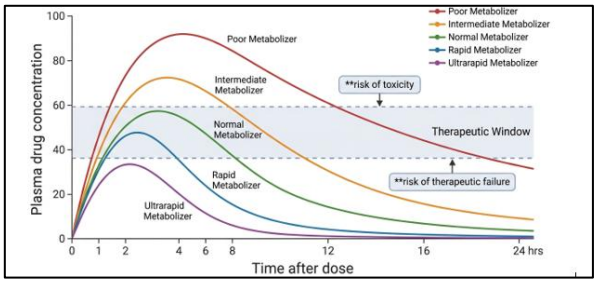
C. Immune-Mediated Hypersensitivity: HLA and Idiosyncratic Reactions

In addition to metabolic enzymes, the human leukocyte antigen (HLA) class I alleles are now well established as markers for immune-mediated, idiosyncratic adverse drug reactions (ADRs), including severe reactions. Other alleles are also associated with adverse drug reactions, including severe reactions to dapsone and co-trimoxazole, as well as to allopurinol and phenytoin (see a complementary mini-review) [25], and have strong ethnicity-dependent allele frequencies, except for classical drug-metabolising enzymes. Table I summarises representative, clinically actionable gene-drug pairs discussed in this section. Figure 2 presents the Cytochrome P450 metabolizer phenotype spectrum and its effect on plasma drug concentration-time profiles.

Table I: Selected Clinically Actionable Pharmacogenes, Associated Drugs, and Guideline-Based Recommendations

Gene	Representative Drug(s)	Key Genotype/Phenotype	Clinical Consequence	Guideline Source (Ref.)
CYP2D6	Beta-blockers (metoprolol, carvedilol); SSRIs	Poor, intermediate, normal, rapid, ultrarapid metabolizer	Altered plasma exposure; risk of bradycardia/hypotension or therapeutic failure	CPIC [15,16]
CYP2C19	Clopidogrel	Loss-of-function alleles (*2, *3) vs *17 gain-of-function	Reduced active metabolite formation; higher risk of stent thrombosis/recurrent MI in PCI patients	CPIC [18]; clinical cohorts [19,20]
CYP2C9 / VKORC1 / CYP4F2	Warfarin	Reduced-function CYP2C9 alleles; VKORC1 promoter variant	Altered maintenance dose requirement; bleeding or sub-therapeutic anticoagulation risk	Population dosing algorithms [21]
DPYD	Fluoropyrimidines (5-FU, capecitabine)	No-function/decreased-function alleles (activity score 0-1.5)	Severe, potentially fatal myelosuppression and GI toxicity if not dose-reduced	CPIC/provincial program [23]
SLCO1B1, ABCG2, CYP2C9	Statins (simvastatin, atorvastatin, rosuvastatin)	Decreased-function SLCO1B1 alleles	Increased systemic exposure; higher risk of statin-associated musculoskeletal symptoms	CPIC [22]
HLA-B*57:01 / HLA-B*15:02 / HLA-A*31:01	Abacavir; carbamazepine	Carrier status for risk allele	Abacavir hypersensitivity; carbamazepine-induced SJS/TEN	HLA-SCAR reviews [24,25]
TPMT / NUDT15	Thiopurines (azathioprine, 6-mercaptopurine)	Reduced/no-function alleles	Severe, dose-dependent myelosuppression	Pharmacogenomic ADR review [25]

SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis; PCI = percutaneous coronary intervention; ADR = adverse drug reaction.



[Fig.2: Cytochrome P450 Metabolizer Phenotype Spectrum and its Effect on Plasma Drug Concentration-Time Profiles]

Sources: Author's Conceptual diagram illustrates the phenotype-exposure relationship central to CYP2D6- and CYP2C19-guided prescribing decisions described in the CPIC beta-blocker from references [15,18,19,20].

IV. APPROACHES TO DRUG RESPONSE PREDICTION: FROM ALGORITHMS TO ARTIFICIAL INTELLIGENCE

A prediction framework is needed to translate genotype into a prescribing decision,

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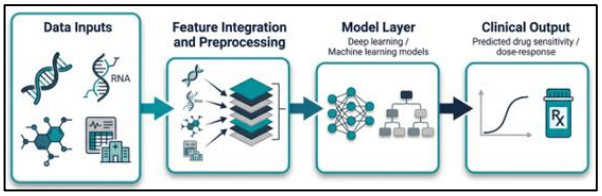
and this sophistication has grown significantly over the review period. At the most basic level, CPIC and DPWG activity score systems use discrete function values for each allele and sum them to the predicted phenotype (e.g., DPYD activity score of 0-2) to provide clear, guideline-supported dosing recommendations that remain the foundation of clinical implementation [3,18,22,23]. To date, multivariable regression algorithms that combine genotype with demographic and clinical covariates have shown better predictive accuracy than clinical factors alone for polygenic, quantitative traits like warfarin dose. However, results differ by ancestry and require local recalibration, as shown in an Iranian validation cohort [21].

The second, rapidly expanding tier uses classic machine-learning methods (random forests, support vector machines, regularised regression) with genomic and transcriptomic data. A comparative assessment of drug response prediction models across 24 individual drugs revealed that comparatively simple and interpretable models, such as ridge regression, can achieve similar performance to more complicated architectures for some drugs, indicating that model complexity does not necessarily provide proportionate benefit, and that explanations of model results are still important for clinical translation [8].

However, the most revolutionary advancement has been using deep learning (DL) to predict multi-omics drug responses, especially in oncology. To predict the sensitivity of cancer cell lines and, more recently, clinical drugs, researchers have used convolutional and graph neural networks, autoencoders, and multimodal fusion architectures to fuse gene expression data, mutation profiles, and drug molecular structures [6,9,10]. In the 2017-2023 timeframe, numerous models were developed for predicting drug response in cancer, with the number of model architectures growing and the predictive performances also improving; however, the authors highlighted the need to overcome the limits of interpretability of the deep learning models, the heterogeneity of the datasets, and the lack of translation of the models from cell-line data to clinical data [9]. Complementary reviews also stress that AI is influencing related areas of clinical pharmacology, such as pharmacovigilance of adverse events, pharmacogenomic variant interpretation, and pharmacokinetic exposure prediction, and that thorough, prospective testing is required before these tools can be integrated into patient management [6,7]. Figure 3 presents the Artificial intelligence/machine learning pipeline for multi-omics-based drug response prediction.



[Fig.3. Artificial Intelligence/Machine Learning Pipeline for Multi-Omics-Based Drug Response Prediction]

Sources: Synthesises deep-learning and multimodal AI pipeline concepts described in references [6,7,9,10].

Unlike the mature, guideline-supported development and use of rule-based pharmacogenomic algorithms, the major hurdles to the widespread use of AI-based prediction tools are external validation, prospective clinical utility studies and regulatory clarity across all three tiers. Table II. compares these methods by data needs, advantages, and disadvantages.

Table II: Comparison of Pharmacogenomic Drug Response Prediction Approaches

Approach	Representative Method	Primary Data Inputs	Strengths	Limitations	Ref.
Rule-based guideline algorithm	CPIC/DPWG activity-score and phenotype tables	Single/multi-gene genotype, diplotype	Transparent, standardised, clinically validated, widely adopted	Limited to well-characterised drug-gene pairs; slow to update for novel variants	[3,15-18,22,23]
Regression-based dosing algorithm	International Warfarin Pharmacogenetics Consortium-type multivariable regression	Genotype + demographic/clinical covariates	Improves dose prediction accuracy over clinical factors alone; population-adaptable	Performance varies across ancestries; requires local recalibration	[21]
Classical machine learning	Random forest, support vector machine, ridge regression	Genomic variants, gene expression, clinical variables	Handles nonlinear interactions; comparable accuracy to deep learning in some tasks; more interpretable	Feature engineering-dependent; moderate sample-size requirements	[8]
Deep learning	Convolutional/graph neural networks, autoencoders	Multi-omics (genomic, transcriptomic), drug structure, cell-line data	Captures complex, high-dimensional relationships; strong performance in cancer drug-response prediction	"Black-box" interpretability; large training data and computational needs; limited external validation	[6,7,9,10]
Integrative multi-omics AI	Multimodal fusion models combining genomics, transcriptomics, and clinical text/EHR data	Combined multi-omics + real-world clinical data	Potential for individualised, dynamic prediction; supports precision oncology and polypharmacy management	Data harmonisation challenges; regulatory and validation gaps; risk of amplifying training-data bias	[6,7,10]

EHR = electronic health record; DPWG = Dutch Pharmacogenetics Working Group

V. PRECISION MEDICINE IMPLEMENTATION: CLINICAL DECISION SUPPORT AND REAL-WORLD PROGRAMS

While scientific evidence is an important factor in driving clinical impact, implementation science and health informatics infrastructure play an equally important role; prolonged global expansion of the use of guidelines over the CPIC's own 15-year retrospective, based on citation tracking, website

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analytics, and member surveys, documents the prolonged global expansion of guideline use over the past 15 years and provides clear evidence of continued diversity in how different health systems implement guidelines in practice [3]. A structured review of pharmacogenomic clinical decision support (CDS) defines and describes the informatics requirements for the point-of-care utility of pharmacogenomic CDS, or the 'five rights' of CDS (right information, right person, right format, right channel, right time), and catalogues interruptive alerts, order entry prompts and structured discrete result reporting as the major technical pathways by which genotype data will be delivered to the prescriber in the electronic health record (EHR) [26].

Feasibility and ongoing conflicts are shown through real-world implementation programs. After piloting the preemptive DPYD testing program at a single centre, the program expanded across British Columbia, where it meaningfully reduced DPYD toxicity and serves as a model for expanding the role of pharmacogenomics in oncology within the public health system [23]. On the other hand, an audit of commercial pharmacogenetic testing vendors and the CPIC guidelines for antidepressant-relevant genes revealed clinically significant discrepancies in how genotype-to-phenotype translation and dosing recommendations were concordant between the vendors, which could lead to different recommendations even with the same genotype data, based on the proprietary algorithms used to interpret the data [14]. Workforce and geographic barriers also complicate the picture: In the United States, pharmacist-led PGx implementation efforts in underserved and rural areas show that PGx education in these settings can measurably increase provider competency and confidence, an identified gap among PGx-trained providers outside large academic medical centres [13].

Real-world implementation studies with multiple genes further support clinical utility. A pragmatic report of pharmacogenomics-guided prescribing in routine outpatient care showed that genotype-derived recommendations influenced prescribing across multiple drug classes, rather than a purely guideline-based approach, and appeared to change prescribing in a way that provided clinical benefit [5]. Table III. summarises the representative implementation programs and the barriers or lessons each highlights.

Table III: Selected Pharmacogenomic Implementation Programs and Barriers to Equitable Adoption

Program/Initiative	Focus Area	Key Feature or Finding	Implication for Precision Medicine	Ref.
Clinical Pharmacogenetics Implementation Consortium (CPIC)	Global guideline development	34 genes and 164 drugs covered by peer-reviewed, evidence-graded guidelines since 2009	Provides the standardised backbone for translating genotype into actionable prescribing decisions worldwide	[3]
BC Cancer province-wide DPYD program (Canada)	Oncology pre-treatment screening	Prospective DPYD genotyping with dose adjustment prevented severe fluoropyrimidine toxicity.	Demonstrates feasibility of scaling preemptive PGx testing across a public health system	[23]
Pharmacogenomic clinical decision support (CDS) frameworks	Health-IT/EHR integration	"Five rights" of CDS; interruptive alerts, order-entry prompts, structured discrete result reporting	Highlights informatics infrastructure required for point-of-care PGx utility	[26]
Rural and underserved workforce PGx education initiatives (USA)	Health equity/workforce training	Pharmacist-led training improved PGx competency in under-resourced settings.	Addresses geographic and workforce-related barriers to equitable implementation	[13]
Commercial vendor vs. CPIC concordance audits	Quality/standardization	Discordant genotype-to-phenotype translation identified between commercial PGx vendors for antidepressants	Underscores need for standardised interpretation to avoid inconsistent prescribing guidance.	[14]
Population/ancestry pharmacogenomic mapping	Diversity and representation	Substantial ethnogeographic variation in actionable allele frequencies; European ancestry over-represented in reference datasets	Calls for broader inclusion of diverse populations in PGx discovery and validation studies	[11,12]

CDS = clinical decision support; EHR = electronic health record; PGx = pharmacogenomics.

VI. CHALLENGES: HEALTH EQUITY, DIVERSITY, AND SYSTEM-LEVEL BARRIERS

The biggest unsolved problem in pharmacogenomics is the limited representation of non-European ancestries in discovery cohorts that underpin allele-function classifications and guideline thresholds. Genetic mapping of population-level variation across the entire continent of Africa and the Middle East and Southeast Asia revealed significant differences in the frequency of alleles associated with an actionable trait, such as variants of G6PD deficiency, that have implications for how genotyping strategies can be effectively and equitably used in different health systems [12]. In a parallel critical review, it is argued that if researchers have not explicitly considered diversity in research, translation, and implementation, pharmacogenomics could further expand existing health disparities, especially those based on race that have carried over from history into modern genomic medicine [11].

These scientific needs add to the practical ones already mentioned: poor consensus around how the commercial tests should be interpreted [14] and limited availability of genotyping and CDS resources outside academic hubs [13,26]. The need for cost-effectiveness and reimbursement mechanisms to support population-level pre-emptive testing was still debated. Editorial summaries of the pharmacogenetics literature reinforce the point that translation barriers remain even where gene-drug pairs are well established, as in infectious diseases and oncology, where standards, awareness, and access to testing do not align with the knowledge base [27,28]. Figure 4 presents the Global disparities in

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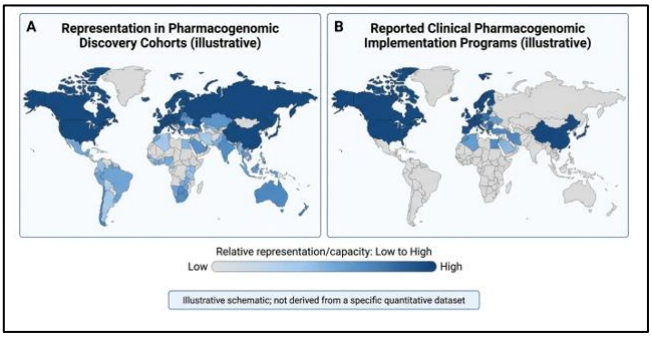
pharmacogenomic research representation and clinical implementation capacity.



[Fig.4: Global Disparities in Pharmacogenomic Research Representation and Clinical Implementation Capacity]

Sources: Data Synthesised from References [11,12].

VII. FUTURE DIRECTIONS

The coming years may feature several tracks for the future direction of pharmacogenomic translation. First, preemptive, panel-based genotyping performed once and stored longitudinally in the electronic health record (EHR) is likely to spread beyond early-adopter academic centres if progress also occurs in CDS infrastructure and standardised result-reporting formats [26]. Second, AI-based methods will be used alongside, not in place of, rules-based approaches, especially for polygenic and multifactorial drug response phenotypes in oncology and psychiatry, with care and only after careful validation in prospective studies that consider algorithm interpretability. [6,7,9,10] Third, intentional efforts to recruit discovery cohorts from diverse ancestries and to invest in the workforce beyond major academic institutions will be critical to ensure that precision medicine does not further benefit already well-resourced populations [11-13]. Lastly, the field needs to harmonise genotype-to-phenotype interpretation, as seen in practice; CPIC and DPWG can help achieve this.

VIII. CONCLUSION

Pharmacogenomics has matured from research into a useful part of precision medicine, supported by dozens of clinically relevant gene-drug combinations across therapeutic areas and endorsed by pharmacogenomics consortia. At the same time, drug response prediction is shifting from simple, rule-based algorithmic models to machine learning and deep learning methods that can capture complex, multi-omic responses to a given drug. However, this scientific advance has yet to be realised in clinical practice because of limitations in informatics infrastructure, a lack of interoperability in commercial interpretation, workforce training gaps, and limited representation of diverse ancestries in the evidence base. This will require coordinated action across clinical, computational, and policy levels to ensure the benefits of genotype-guided and personalised drug therapy reach a large population, not only the best candidates.

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- **Ethical Approval and Consent to Participate:** The content of this article does not necessitate ethical approval or consent to participate, with supporting documentation.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Authors' Contributions:** The authorship of this article is contributed equally to all participating individuals.

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