

Chapter 9

Genes, Machines, and Healing-The New Era of Personalised Medicine: A Comprehensive Review on AI-Driven Pharmacogenomics

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Abstract: Pharmacogenomics, or the study of how genetic variation influences drug response, has emerged as a key component of precision medicine. By integrating genomic science with clinical pharmacology, pharmacogenomics enables individualized drug therapy that maximizes therapeutic benefit while minimizing adverse effects. Recent advances in artificial intelligence (AI), machine learning, multi-omics, and digital health technologies have accelerated the translation of genomic insights into real-world clinical practice. This manuscript reviews in depth the principles, clinical applications, and future perspectives of AI-driven pharmacogenomics, supported by a case study illustrating the practical relevance of genotype-guided therapy. Covering major drug-gene interactions, including CYP2C9/VKORC1-warfarin, CYP2C19-clopidogrel, HLA pharmacogenomics, oncology biomarkers, and psychopharmacology, the review discusses the transformative potential and challenges to be considered in translating pharmacogenetic testing into routine care. Ethical considerations, infrastructural limitations, and genomic diversity issues are discussed, along with emerging opportunities like AI-enabled decision support, automated genomic interpretation, and precision dosing platforms. The manuscript concludes with recommendations for improving pharmacogenomic adoption in countries.

Keywords: Pharmacogenomics, Personalized Medicine, Artificial Intelligence, Genomics, Warfarin, CYP450, Precision Medicine, Machine Learning, Drug Response

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Introduction

Despite major advances in therapeutics, modern healthcare continues to rely on a one-dose-fits-all paradigm that fails to account for genetic variability among patients. As a result, significant interindividual differences in drug response persist, leading to suboptimal outcomes, unexpected toxicities, and preventable adverse drug reactions (ADRs). ADRs remain a major cause of hospitalizations worldwide, particularly with high-risk medications such as anticoagulants, antiplatelets, antiepileptics, and psychotropics. Although critical drug–gene associations such as CYP2C9/VKORC1 with warfarin, CYP2C19 with clopidogrel, and HLA-B*1502 with carbamazepine are well established, they remain underutilized in routine practice. (1)

Compounding this challenge are real-world complexities, including polypharmacy, chronic comorbidities, and diverse genetic backgrounds. Many clinicians lack the time, training, and resources required to interpret genomic data, resulting in trial-and-error prescribing, longer treatment cycles, and higher healthcare costs. The increasing volume and complexity of genomic datasets have outpaced the capabilities of traditional analytical methods, emphasizing the need for advanced computational solutions. (2)

Pharmacogenomics provides a pathway to precision medicine by integrating genetic information into drug therapy to improve safety and efficacy. To optimize these benefits, clinicians require decision-support systems capable of rapidly analysing genomic data. Artificial intelligence (AI) and machine learning (ML) offer powerful tools to identify complex drug–gene interactions, predict individualized outcomes, and support real-time precision dosing. (2)

This manuscript reviews the current landscape of AI-driven pharmacogenomics, highlighting its clinical value through evidence-based examples such as warfarin sensitivity, clopidogrel resistance, HER2-targeted therapies, and psychiatric pharmacogenomics. A case study of a patient with exaggerated warfarin response illustrates the practical importance of genotype-guided care.

By synthesizing contemporary research and technological advancements, this work emphasizes the need to expand pharmacogenomics adoption globally. Ultimately, AI-enabled pharmacogenomics has the potential to become an essential component of clinical practice, promoting safer, more effective, and personalized healthcare.

1.1 Genetics and Genomics: Foundational Concepts

Genetics is the study of genes and heredity how traits and biological characteristics are transmitted from generation to generation. It focuses primarily on individual genes and their specific functions.

Genomics, in contrast, is the comprehensive analysis of the entire genome, including gene–gene interactions, structural variations, epigenetic modifications, and regulatory networks. Genomics provides a systems-level understanding of disease mechanisms and drug responses. (3)

The advent of whole-genome sequencing, next-generation sequencing (NGS), transcriptomics, proteomics, and metabolomics has expanded the scope of traditional genetics to multi-omics-guided personalized medicine. (4)

1.2 Pharmacogenomics: Linking Genes to Drug Response

Pharmacogenomics bridges pharmacology and genomics to explain interindividual variation in drug pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics (drug–receptor interactions).

Three categories of pharmacogenomic determinants are especially crucial:

1. Drug-metabolizing enzymes

Drug-metabolizing enzymes (DMEs) are biological enzymes in the body primarily found in the liver that chemically modify (metabolize) medications so they can be used, inactivated, or safely eliminated. They play a central role in determining how quickly a drug is broken down, how long it stays active, and how strongly it affects the body. Genetic polymorphisms alter metabolic capacity, influencing toxicity and therapeutic efficacy.(5)

2. Drug transporters

Drug transporters are specialized proteins located on cell membranes that control the movement of drugs into and out of cells. They determine how a drug is absorbed, distributed, and eliminated, and therefore play a major role in drug effectiveness and safety.(6)

3. Drug targets

Drug targets are specific molecules in the body usually proteins that a drug interacts with to produce its therapeutic effect. They are the sites where drugs bind and initiate biological changes. Receptors, enzymes, ion channels, or structural proteins are directly involved in drug action. Variants can cause altered drug sensitivity or resistance.(7)

2. Key Components of Pharmacogenomics

2.1 Cytochrome P450 (CYP450) Enzymes

Approximately 70% of all clinically used medications are metabolized by CYP450 enzymes. People are classified as poor, intermediate, normal (extensive), or ultra-rapid metabolizers based on genetic variations in these enzymes, which changes drug levels and side effect risk. For example, CYP2C19 *2 and *3 loss-of-function variants decrease the activation of clopidogrel, and CYP2C9 *2 and *3 variants slow the metabolism of warfarin.(8)

2.2 Drug Transporters

Because ABCB1 genetic variation affects how drugs are transported across cell membranes, it can change how many medications, such as antidepressants, chemotherapies, and antivirals, are handled. Because SLCO1B1 variants increase systemic exposure by decreasing hepatic uptake of statins, they are strongly associated with an increased risk of statin-induced myopathy.

2.3 Drug Targets

Patients who are likely to benefit from trastuzumab are identified by HER2 gene amplification, and VKORC1 variants reduce warfarin sensitivity. When combined, these genomic markers help inform more individualized and accurate treatment choices.

3. Clinical Implications of Pharmacogenomics

3.1 Personalized Drug Therapy

In the context of pharmacogenomics, personalized medicine means adjusting drug therapy to fit an individual's unique genetic profile. Pharmacogenomics studies the impact of variations in genes, especially those responsible for encoding drug-metabolizing enzymes, drug transporters, and drug targets, on a patient's response to medication. Clinicians can use this type of genetic information, integrated with clinical judgment, to predict whether a patient is likely to derive a benefit from a drug, needs a modified dose, or may suffer from adverse drug reactions.

Pharmacogenomics enables clinicians to tailor drug therapy based on individual genetic profiles, achieving:

- optimal drug selection
 - enhanced therapeutic outcomes
 - reduced trial-and-error prescribing
1. **Optimal drug selection:** choosing the right medication, dose, and timing for an individual based on their genetic makeup, clinical profile, and context aiming to maximize efficacy, minimize toxicity, and respect patient preferences. At its core, it integrates pharmacogenomic data with clinical decision making to tailor therapy rather than relying solely on population averages(9)
 2. **Enhanced therapeutic outcomes:** refers to measurable improvements in how well a treatment works for a specific individual when drug choice, dose, and timing are tailored to their genetic variants, disease biomarkers, physiology, comorbidities, and concomitant medications. In practice, personalization yields higher efficacy, fewer adverse drug reactions, faster achievement of therapeutic targets, and better real-world adherence and persistence ultimately improving survival, symptom control, and quality of life.(10)
 3. **Reduced trial-and-error prescribing:** One of the most important benefits of personalized drug therapy is the reduction of trial-and-error prescribing. Traditionally, clinicians often cycle through multiple drugs before finding one that works for a patient, especially in areas like psychiatry, cardiology, and oncology. Personalized approaches using pharmacogenomics, biomarkers, and clinical decision support help select the right drug and dose from the start, minimizing wasted time, adverse events, and patient frustration.

3.2 Reduction of Adverse Drug Reactions (ADRs)

ADRs account for significant morbidity and healthcare costs. Genetic testing can prevent life-threatening reactions for instance:

- HLA-B*1502–associated Stevens–Johnson syndrome with carbamazepine(11)
- CYP2C9/VKORC1–associated warfarin bleeding
- SLCO1B1-associated statin-induced rhabdomyolysis(12)

1. HLA-B*1502–associated Stevens–Johnson syndrome with carbamazepine:

Action: Screen for HLA-B*15:02 prior to initiating carbamazepine in populations with higher allele prevalence (many Asian ancestries, including Indian).

Rationale: Carriers have markedly increased risk of SJS/TEN.

2. CYP2C9/VKORC1-associated warfarin bleeding

Action: Obtain CYP2C9 (*2, *3) and VKORC1 (-1639G>A) before or at initiation; use validated algorithms (e.g., Gage, IWPC) integrating genotype plus clinical factors.

Rationale: Poor metabolizers/sensitive genotypes need lower initial doses to avoid over-anticoagulation.

3. SLCO1B1-associated statin-induced rhabdomyolysis:

Action: Test SLCO1B1 c.521T>C (rs4149056) before high-risk statins (especially simvastatin \geq 20–40 mg).

Rationale: Reduced OATP1B1 function increases statin exposure and myopathy risk.

3.3 Optimized Drug Dosing : Genotype-guided dosing improves precision by aligning starting dose, titration speed, and monitoring intensity to a patient's pharmacogenomic profile. This is most impactful for narrow-therapeutic-index drugs where small exposure changes cause loss of efficacy or toxicity such as

- warfarin
- phenytoin
- immunosuppressants
- anticancer drugs

3.4 Enhanced Neurological and Psychiatric Care

• Antidepressants and Antipsychotics

Genes involved: CYP2D6, CYP2C19, SLC6A4, HTR2A.

Impact: Variants in CYP2D6 and CYP2C19 affect metabolism of SSRIs, SNRIs, and tricyclic antidepressants. Poor metabolizers risk toxicity at standard doses; ultra-rapid metabolizers may have subtherapeutic levels.

Clinical benefit: Pharmacogenomic testing guides dose adjustments or alternative drug choice, improving remission rates and reducing side effects.

• Mood Stabilizers and Anticonvulsants

Carbamazepine and Phenytoin: HLA-B15:02* strongly associated with Stevens–Johnson syndrome/toxic epidermal necrolysis in Asian populations. CYP2C9 variants reduce phenytoin clearance, increasing risk of toxicity.

Clinical benefit: Genetic screening before prescribing prevents life-threatening ADRs.

AI-driven pharmacogenomics and multi-omics provide new tools to improve therapy selection.

4. Clinical Pharmacogenomics of Common Drugs

4.1 Warfarin: CYP2C9 and VKORC1

Warfarin (CYP2C9 & VKORC1): Genetic variations have a significant impact on warfarin dosage. While VKORC1-1639G>A variants increase sensitivity to warfarin, necessitating lower doses, CYP2C9 variants decrease metabolism, resulting in higher drug levels and increased risk of bleeding. Warfarin is a prime example of pharmacogenomic precision therapy, with genotype-guided dosing reducing hospitalizations due to bleeding or thromboembolic events by 43%.⁽¹³⁾

4.2 Clopidogrel: CYP2C19

CYP2C19 is necessary for the activation of clopidogrel. People with poor-metabolizer genotypes produce less active medication, which increases their risk of myocardial infarction, ischemic complications, and stent thrombosis. For better results, pharmacogenomic testing suggests moving to substitutes like ticagrelor or prasugrel.

4.3 Psychiatry: Multi-omics-Driven Precision Medicine

AI and pharmacogenomics combined in psychiatry allow for more individualized care. Machine learning models forecast medication response, and AI-assisted antidepressant selection can cut side effects by 30 to 50%. Real-time algorithms dynamically modify treatment, and natural language processing (NLP) tools extract clinical predictors from electronic health records. These advancements support precision therapy in depression, bipolar disorder, and schizophrenia.(14)

5. Additional Clinical Applications

5.1 Oncology: HER2 and Targeted Therapy

About 20–25% of breast cancers have HER2 amplification, which promotes rapid tumor growth. By inhibiting the HER2 receptor's signaling, trastuzumab slows the growth of tumors. A number of targeted treatments, such as EGFR, ALK, BRAF/MEK, and PARP inhibitors, have been made possible by developments in genomic profiling. AI-based models are increasingly assisting oncology by predicting pertinent biomarkers and matching patients with suitable targeted treatments.(15)

5.2 Infectious Diseases: COVID-19

By directing the use of remdesivir, optimizing corticosteroid dosage, predicting a person's risk of cytokine storm, and identifying host genetic factors that affect antiviral response, pharmacogenomics helps customize COVID-19 therapy.

6. Artificial Intelligence in Pharmacogenomics

AI in pharmacogenomics employs sophisticated algorithms to evaluate genetic information, forecast medication reactions, and direct individualized treatment. It supports dose optimization, predicts drug efficacy and toxicity, finds novel gene-drug interactions, and identifies clinically significant genetic variants. AI-powered decision-making tools combine clinical and genomic data to suggest safer, more efficient therapies. In general, AI speeds up precision medicine by improving the speed, accuracy, and clinical actionability of pharmacogenomic insights.(1)

6.1 Artificial intelligence tools in pharmacogenomics

Whole-genome and whole-exome sequencing is affordable with Next-Generation Sequencing (NGS), which makes it possible to quickly identify both common and uncommon pharmacogenomic variants with shorter turnaround times. Implementation is further supported by bioinformatics tools such as Pharm CAT, which translates genetic results into CPIC-aligned recommendations for consistent interpretation, CPIC, which provides standardized evidence-based prescribing guidelines with defined evidence levels, and PharmGKB, which gathers important gene-drug relationships. Integration of pharmacogenomic data into Electronic Health Records (EHRs) enhances clinical decision support by providing real-time drug–gene alerts, automated dose adjustments, and improved workflow efficiency through pre-emptive genotyping.

Additionally, wearable technology such as smartwatches and smartphone apps contributes ongoing digital biomarkers that allow for AI-driven early treatment effect detection and customized dose optimization. (16)

Predicting Drug Response and Toxicity

To produce predictive insights, machine learning models combine genomic data, demographic information, clinical biomarkers, and drug-drug interaction profiles. These models are used to predict outcomes like chemotherapy efficacy, immunotherapy-related toxicities, and antidepressant response.(14)

Automating Genomic Data Interpretation

AI tools greatly lessen the workload for geneticists and clinicians by effectively analyzing whole-genome and whole-exome sequencing data, SNP arrays, structural variants, and gene expression profiles.

AI-Driven Drug Discovery and Repurposing

AI-driven drug discovery and repurposing uses tools such as structure-based drug design, target prediction models, virtual screening, and repurposing platforms to speed up pharmacogenomic research and support faster biomarker identification.

Polygenic Risk Scoring (PRS)

To determine a person's risk for diseases like diabetes, heart disease, neurological disorders, and mental illnesses, Polygenic Risk Scoring (PRS) integrates thousands of SNPs. PRS enhances precision prevention and individualized healthcare approaches when combined with pharmacogenomics.(17)

AI-Enabled Clinical Decision Support

AI-powered clinical decision support systems can reduce prescription errors, dynamically modify dosage, integrate with EHRs to deliver real-time alerts, and suggest the best medications, all of which increase the overall efficiency of clinical workflow. (18)

7. Current Challenges and Barriers

Despite advances, pharmacogenomics faces obstacles:

7.1 Technical Challenges

Biases in AI models resulting from training datasets that overrepresent European ancestry despite diverse pharmacogenomic allele frequencies, which reduce utility in underrepresented populations; poor data quality and interoperability due to unstructured, heterogeneous healthcare data, variable formats across institutions, and the lack of standardized exchange protocols; and limited model interpretability, as deep learning systems function as "black boxes," with evolving explainable AI methods and a continuous need for clearer mechanistic understanding of predictions, all contribute to the difficulties in applying AI to pharmacogenomics.(19)

7.2 Clinical Implementation Barriers

Since the FDA is now regulating laboratory-developed tests (LDTs) as medical devices and imposing stricter approval requirements that may restrict test availability and raise costs while the regulatory pathway continues to evolve, regulatory uncertainty presents significant challenges in pharmacogenomics. Additionally, turnaround time is crucial; in order to preserve clinical utility, results must be accessible within 24 hours, requiring smooth integration with electronic prescribing systems. Furthermore, there are still concerns regarding clinical utility because there is insufficient evidence for

many gene-drug combinations. For instance, the INGENIOUS trial showed challenges when decision support was insufficient, highlighting the need for larger prospective validation studies to establish robust clinical benefit.(20)

7.3 Equity and Access Issues

Lack of universal insurance coverage for pharmacogenomic testing, socioeconomic barriers that limit access, and a lack of genetic data from diverse populations are the main causes of healthcare disparities in pharmacogenomics. The problem is made more difficult by the discovery of thousands of uncommon genetic variations using next-generation sequencing (NGS) technologies, whose functional significance is frequently unknown. This makes it challenging to produce enough clinical evidence to support individualized treatment choices.(21)

7.4 Ethical, Legal, and Social Issues (ELSI)

Concerns regarding the storage and secondary use of sensitive genetic data are raised by genetic privacy in pharmacogenomics, necessitating stringent adherence to laws like GDPR and HIPAA as well as handling incidental results from genetic testing. Since patients might not fully comprehend the implications of genetic testing, informed consent is still a crucial issue, underscoring the necessity of easily accessible genetic counseling resources. There are also possible risks of discrimination, such as employment bias based on a person's pharmacogenomic profile and insurance coverage restrictions.(19)

7.5 Data Privacy and Security

Because genomic data are extremely sensitive and personally identifiable, they are susceptible to cybersecurity risks and possible data breaches, making data privacy and security in pharmacogenomics essential. Strict adherence to laws like PIPEDA, GDPR, and HIPAA is necessary to ensure strong protection, protect patient data, and preserve confidence in genomic healthcare applications.(20)

7.6 Regulatory Challenges

The regulatory challenges associated with implementing AI in pharmacogenomics stem from the evolving oversight of genetic tests and AI tools. Laboratory-developed tests (LDTs) are now subject to FDA regulation as medical devices, with more stringent approval requirements that may restrict test availability and raise costs. Due to "black box" models that are difficult to understand, regulatory pathways for AI algorithms are still unclear. Due to sensitive genomic data, adherence to data privacy laws like HIPAA, GDPR, and PIPEDA is crucial. Adoption is further complicated by the lack of clinical evidence for many gene-drug combinations, highlighting the necessity of prospective validation studies to guarantee safety, accuracy, and clinical utility.(20)

8. Future Directions

New developments in precision medicine suggest that newborn genetic screening will be expanded, allowing for the earlier identification of inherited disorders and more successful preventive measures. A deeper, systems-level understanding of how genes, environment, and lifestyle all influence drug responses will be possible through the integration of multi-omics and exposomics. The identification of population-specific genetic variants and the generalizability of pharmacogenomic results will be further

improved by global biobank-driven insights. Federated learning and other privacy-preserving AI techniques will enable safe, extensive data sharing without jeopardizing patient privacy. Furthermore, the creation of digital twins—virtual copies of specific patients—promises to mimic medication reactions prior to clinical application. Lastly, individualized polypharmacy management tools will help improve therapeutic outcomes, minimize adverse drug reactions, and optimize medication regimens for patients with complex treatment needs.(22)

9. Conclusion

AI-driven pharmacogenomics represents a critical transition from population-based prescribing to data-driven, truly personalized medicine. Pharmacogenomics enables accurate drug selection, safer dosing, and a significant decrease in adverse drug reactions—one of the most avoidable burdens on global healthcare—by combining genomic data with clinical, environmental, and behavioral factors. By automating genomic interpretation, identifying intricate drug-gene and gene-environment interactions, and providing real-time clinical decision support, artificial intelligence enhances these advantages. Genotype-guided therapy consistently improves outcomes, increases safety, and lowers healthcare costs, according to evidence from cardiology, oncology, psychiatry, infectious diseases, and neurology.

Despite this development, there are still many obstacles to overcome. Widespread clinical integration is still hampered by a lack of genomic diversity in current datasets, changing legal frameworks, ethical privacy concerns, and unequal access to testing. Global standardization, strong prospective clinical trials, fair testing access, and legislative frameworks that promote the ethical and safe application of genomic and artificial intelligence technologies are all necessary to overcome these obstacles. It will be crucial for clinicians, geneticists, data scientists, regulatory agencies, and legislators to work together across disciplinary boundaries.

Future developments in precision medicine include digital twins, federated learning, multi-omics integration, global biobank expansion, and AI-enabled polypharmacy optimization. AI-driven pharmacogenomics has the potential to become a standard part of healthcare as these technologies advance, guaranteeing that each patient receives the appropriate medication at the appropriate dosage at the appropriate time. In the end, the combination of genes and intelligent machines is a revolutionary step toward safer, more intelligent, and more personalized healing rather than merely an advancement in therapeutics.

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