

GENETIC SIGNATURES IN DRUG RESPONSE: THE PAST, PRESENT, AND FUTURE OF PHARMACOGENOMICS

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ABSTRACT

Pharmacogenomics is redefining therapeutics by linking genetic variation to interindividual differences in drug efficacy and safety. Unlike the traditional “one-size-fits-all” approach, pharmacogenomics emphasizes precision, where allelic variants in drug-metabolizing enzymes, transporters, and molecular targets dictate clinical outcomes. Classic examples of CYP polymorphism include 1) CYP2C19 is required for the bioactivation of clopidogrel, with poor metabolizers experiencing increased thrombotic risk, and 2) CYP2D6 ultra-rapid metabolizers convert codeine to morphine at toxic levels.

Beyond metabolism, HLA alleles provide striking illustrations: 1) HLA-B*57:01 screening is mandated before abacavir to prevent hypersensitivity. 2) HLA-B*15:02 testing avoids carbamazepine-induced Stevens–Johnson syndrome in Asian populations.

Oncology has emerged as the leading paradigm of pharmacogenomics, where the identification of actionable genomic alterations increasingly defines precision medicine. Examples, in non-small cell lung cancer (NSCLC), activating EGFR mutations or ALK gene rearrangements serve as critical biomarkers that predict responsiveness to specific tyrosine kinase inhibitors, improving patient outcomes compared with conventional chemotherapy. Beyond solid tumors, pharmacogenomics has also transformed haematological malignancies. Variants in TPMT (thiopurine S-methyltransferase) and NUDT15 (Nudix hydrolase 15) genes critically influence the inactivation of thiopurines such as mercaptopurine, which is the mainstay of therapy in acute lymphoblastic leukemia. Patients with reduced or absent enzyme activity are at high risk of severe, potentially life-threatening myelotoxicity if treated with standard doses. Preemptive genetic testing for these polymorphisms allows for dose adjustments tailored to an individual's metabolic capacity, thereby maximizing therapeutic efficacy while minimizing toxicity. At the next level, whole-exome and whole-genome sequencing (WES/WGS) are being integrated into clinical practice. Commercial platforms such as GeneSight and OneOme RightMed deliver multi-gene panels across psychiatry, cardiology, oncology, and pain medicine. By individualizing therapy, reducing adverse events, and maximizing therapeutic benefit, it is rapidly becoming a cornerstone of precision medicine.

INTRODUCTION

Patients receiving the same medication often exhibit markedly different therapeutic outcomes. While some achieve optimal clinical benefit, others experience treatment failure or develop adverse drug reactions (ADRs), ranging from mild intolerance to

life-threatening toxicity. These differences arise from a complex interplay of drug-related factors, environmental influences, disease states, and genetic variation.^[1]

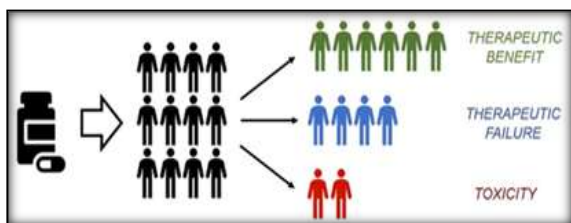


Figure 1: Therapeutic effects, failure, and adverse effects due to drugs

Pharmacogenomics (PGx) is the study of how genetic variation across the genome influences drug response. By identifying genetic determinants of drug efficacy, toxicity, and dosage requirements, pharmacogenomics aims to move clinical practice away from the traditional "one-size-fits-all" approach toward precision medicine, in which therapy is tailored to an individual's genetic profile.^[2]

Genetic variants can influence:

- Drug absorption and transport
- Drug metabolism
- Drug targets and signaling pathways
- Immune-mediated adverse drug reactions

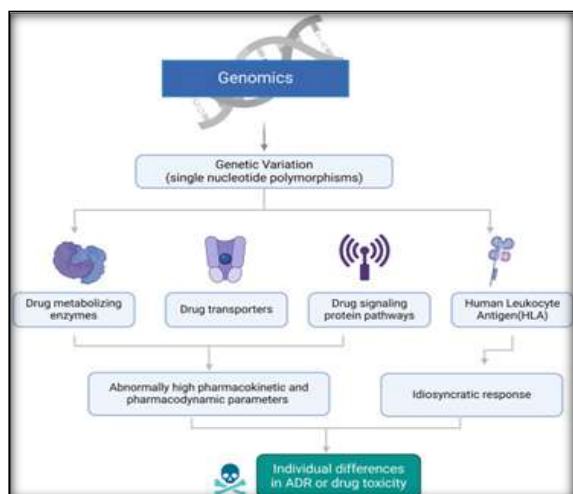


Figure 2: Genomics affecting drug response through various targets

As genomic technologies become increasingly accessible, pharmacogenomics is emerging as a cornerstone of individualized therapeutics.^[3]

Pharmacogenetics versus Pharmacogenomics

Although often used interchangeably, pharmacogenetics and pharmacogenomics differ in scope.

Pharmacogenetics

Pharmacogenetics examines the effect of variation in a single gene on drug response.

Examples include:

- CYP2D6 and codeine
- TPMT and thiopurines
- HLA-B*57:01 and abacavir

Pharmacogenomics

Pharmacogenomics evaluates the influence of multiple genes and genome-wide variation on drug response.

Examples include:

- Warfarin dosing algorithms incorporating CYP2C9, VKORC1, CYP4F2, age, and ancestry
- Tumor genomic profiling to guide targeted cancer therapies
- Polygenic prediction models for therapeutic response

Thus, pharmacogenomics represents a broader, systems-level approach to precision medicine.

Personalized Medicine, Precision Medicine, and Pharmacogenomics

Personalized medicine considers all patient-specific characteristics, including:

- Genetics
- Age
- Sex
- Body weight
- Diet
- Lifestyle
- Comorbidities

Personalized medicine = Genetics + Comorbid conditions + individual factors.

E.g, Bronchial asthma treatment: In pediatric patients, severe asthma is frequently driven by specific allergic pathways (Type 2 inflammation). A child may be prescribed targeted monoclonal antibodies like Omalizumab early on. Conversely, in older adults, asthma is often non-allergic and heavily compounded by smoking or occupational exposures, requiring a shift toward personalized long-acting bronchodilator therapies rather than allergy biologics.^[4]

Precision medicine focuses on stratifying patients into biologically defined subgroups to optimize treatment selection.^[5]

Precision medicine = Biomarkers-guided patient stratification.

E.g, HER2 +ve in Breast Cancer will receive trastuzumab; BRCA1 and BRCA2 Mutations in Ovarian/Breast Cancer will benefit from PARP inhibitors (e.g., olaparib).

Pharmacogenomics is a key component of precision medicine that specifically relates genomic variation to drug response.

Pharmacogenomics = Drug + Gene interaction. E.g, CYP2C19 poor metabolizers should not receive clopidogrel and recommend alternative ticagrelor.

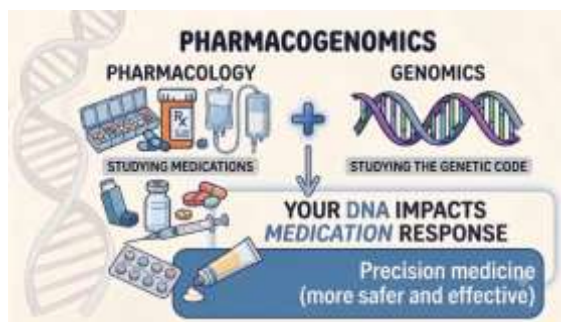


Figure 3: Pharmacogenomics

Historical Evolution of Pharmacogenomics:

The origins of pharmacogenomics can be traced back more than 2,500 years.

Early observations

Around the 5th century BC, Pythagoras observed that consumption of fava beans caused illness in some individuals but not others. This phenomenon is now known to result from glucose-6-phosphate dehydrogenase (G6PD) deficiency.^[6,-8]

Mid-20th century discoveries

Several genetically determined drug responses were subsequently identified:

- Hemolysis following antimalarial therapy in individuals with G6PD deficiency
- Prolonged paralysis after succinylcholine due to pseudocholinesterase deficiency
- Malignant hyperthermia associated with volatile anesthetics and RYR1 mutations

Genomic era

The sequencing of the human genome and advances in genome-wide association studies (GWAS) accelerated the discovery of clinically relevant pharmacogenes.

Today, pharmacogenomics encompasses:

- Drug-metabolizing enzymes: CYP2D6, CYP2C19.
- Drug transporters: SLCO1B1
- Drug targets: VKORC1
- HLA alleles: HLA-B*57:01

Genetic Determinants of Drug Response

Drug response is influenced by genetic variation affecting pharmacokinetics, pharmacodynamics, and immune function.^[9,10]

Pharmacokinetic Variants

Drug Transporters

- SLCO1B1 variants increase simvastatin-associated myopathy risk.

Drug-Metabolizing Enzymes

- CYP2D6 and codeine
- CYP2C19 and clopidogrel
- TPMT and thiopurines
- CYP2C9 and warfarin

Pharmacodynamic Variants

Variants in drug targets may alter therapeutic response.

Examples:

- VKORC1 and warfarin sensitivity
- EGFR mutations and gefitinib response
- HER2 amplification and trastuzumab response
- BRAF mutations and vemurafenib response

Immune-Mediated Variants

HLA alleles strongly predict severe adverse drug reactions.^[11-13]

Examples:

Drug	Genetic Marker	Clinical Outcome
Abacavir	HLA-B*57:01	Hypersensitivity
Carbamazepine	HLA-B*15:02	Stevens-Johnson syndrome
Allopurinol	HLA-B*58:01	Severe cutaneous reactions
Phenytoin	HLA-B*15:02	Stevens-Johnson syndrome

Genotype, Star Alleles, and Phenotype

Understanding pharmacogenomics requires distinguishing genotype from phenotype.^[14]

Allele

An allele represents a variant form of a gene inherited from each parent.

Haplotype and Star Alleles

A haplotype is a set of linked genetic variants inherited together.

The star (*) allele nomenclature is commonly used for CYP enzymes.

Examples:

- CYP2C19*1 = normal function
- CYP2C19*2 = loss-of-function
- CYP2C19*3 = loss-of-function

Genotype

The combination of two inherited alleles.

Examples:

- *1/*1
- *1/*2
- *2/*2

Phenotype

The resulting functional activity.

Genotype	Phenotype
*1/*1	Normal metabolizer
*1/*2	Intermediate metabolizer
*2/*2	Poor metabolizer

Table 1: Genotype, haplotype and phenotype

Genotype (SNP)	Haplotype (* allele)	Phenotype
GG (normal)	*1*1	Normal metabolizer
GA	*1*2	Intermediate metabolizer
AA	*2*2	Poor metabolizer
GG looks at only one SNP (two haplotypes)		
*1/*1 represents the entire gene's functional status (haplotypes)		

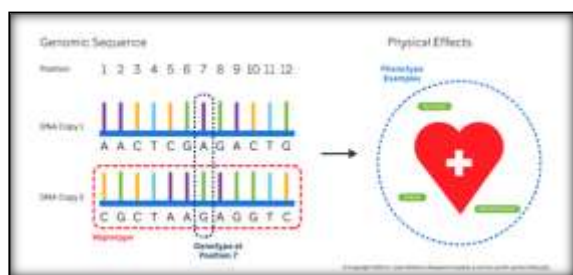


Figure 4: Genotype and haplotype.^[32,33]

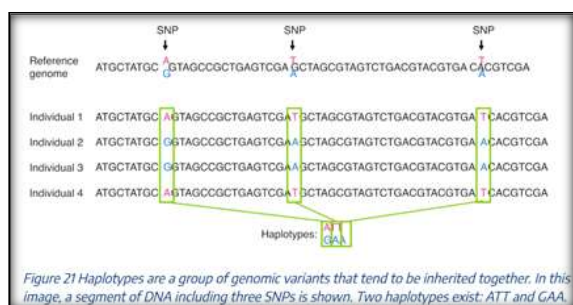


Figure 5: Haplotype.^[32,33]

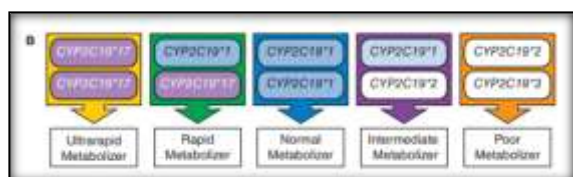


Figure 6: Phenotype.^[32]

For CYP2D6, additional categories include:

- Ultrarapid metabolizer
- Rapid metabolizer
- Normal metabolizer
- Intermediate metabolizer
- Poor metabolizer

Clinical Benefits of Pharmacogenomic Testing

A pre-emptive 12-gene pharmacogenetic panel significantly reduced clinically relevant adverse drug reactions and demonstrated that panel-based pharmacogenomic testing can improve drug safety in routine clinical practice.^[15,16]

Pharmacogenomic testing can improve patient care by:

A. Improving Drug Safety: Preventing severe adverse drug reactions.

Examples:

- HLA-B*57:01 and abacavir
- HLA-B*15:02 and carbamazepine

B. Optimizing Drug Efficacy

Examples:

- CYP2C19-guided antiplatelet therapy
- EGFR-directed lung cancer treatment

C. Individualizing Drug Dosing

Examples:

- Warfarin
- Thiopurines
- Tacrolimus

D. Reducing Trial-and-Error Prescribing

Pharmacogenomics shortens the therapeutic odyssey by selecting effective therapies earlier.

E. Supporting Drug Development

Genetic biomarkers facilitate:

- Target identification
- Patient selection
- Companion diagnostics
- Precision clinical trials

Pre-emptive and Reactive Pharmacogenomic Testing

In the US, five medical centers had successfully implemented preemptive pharmacogenetic testing, where patients are genotyped before a drug is prescribed and the results are stored in the electronic health record for future use.^[17]

Pre-emptive Testing: Genetic information is obtained before drug exposure.

Examples:

- HLA-B*57:01 before abacavir
- Multi-gene pharmacogenomic panels

Advantages:

- Lifelong utility
- Immediate availability
- Prevention of toxicity

Reactive Testing: Relling and Klein established the Clinical Pharmacogenetics Implementation Consortium (CPIC) to facilitate the translation of genetic test results into prescribing decisions.^[18]

Testing is performed after treatment failure or adverse reactions.

Examples:

- TPMT testing after thiopurine-induced myelosuppression.

Although reactive testing remains common, healthcare systems are increasingly adopting pre-emptive testing strategies.

Pharmacogenomics in Oncology

Oncology represents one of the earliest and most successful applications of pharmacogenomics. Germline genetic variants in TPMT, NUDT15, DPYD, and UGT1A1 significantly influence the toxicity of thiopurines, fluoropyrimidines, and irinotecan. Genotype-guided dosing can prevent life-threatening adverse effects while maintaining therapeutic efficacy, making pharmacogenomics a key component of precision oncology.

Oncology represents the most successful implementation of precision medicine.^[19-21]

Examples include:

Non-Small Cell Lung Cancer

- EGFR mutations → EGFR inhibitors (Gefitinib)
- ALK rearrangements → ALK inhibitors (Alectinib)

Breast Cancer

- HER2 amplification → Trastuzumab

Colorectal Cancer

- KRAS wild-type tumors → Anti-EGFR therapy

Acute Leukemia

- TPMT and NUDT15 variants guide thiopurine dosing.

These approaches maximize efficacy while minimizing toxicity

Pharmacogenomics beyond Oncology: Cystic Fibrosis as a Paradigm

Cystic fibrosis illustrates how understanding disease genetics can transform therapeutics.

The Wainwright et al. 2015 study transformed cystic fibrosis therapy from symptomatic management to genotype-directed treatment, providing one of the clearest early demonstrations that correcting a disease-causing protein defect can improve clinical outcomes in a genetic disorder.^[22]

CFTR mutations disrupt chloride transport, producing:

- Thick airway secretions (airways)
- Elevated sweat chloride concentrations

Treatment selection depends on the underlying CFTR mutation, representing a striking example of genotype-guided therapy.

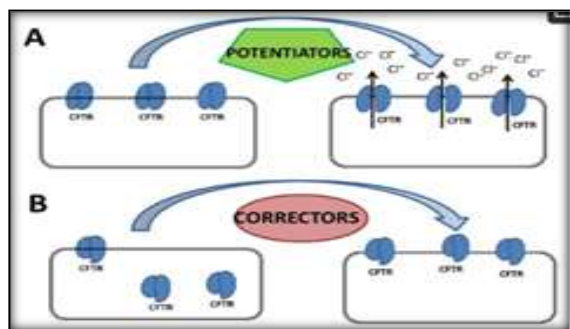
Targeted therapies include:

Potentiators

- Ivacaftor
- Improve CFTR channel opening

Correctors

- Lumacaftor
- Tezacaftor
- Improve trafficking of CFTR to the cell surface



Implementation Resources and Clinical Decision Support

Whirl-Carrillo et al. developed the standardized evidence-scoring framework that underpins PharmGKB clinical annotations, providing a transparent and reproducible method for translating pharmacogenomic research into clinically actionable knowledge.^[23]

Important pharmacogenomic resources include:

- PharmGKB
- CPIC
- PharmCAT
- ClinPGx

Integration of pharmacogenomic information into electronic health records with clinical decision support systems is enabling real-time prescribing recommendations. ClinPGx (formerly PharmGKB) Drug Label Classifications for Pharmacogenomics

ClinPGx classifies pharmacogenomic information in drug labels into four major categories. These categories help determine whether a gene-drug interaction is clinically actionable and whether genetic testing should be performed before prescribing. Drug labels are divided into the following categories based on genetic testing.

Drug examples under each drug label category vary depending on different countries' health regulators, like the FDA, EMA, HSCS, DPWG, PMDA, and Swissmedic.

Table 2: Classification of pharmacogenomic testing as per Clinical Actionability (ClinPGx)

ClinPGx Level	Meaning	Clinical Significance	Examples
Testing Required	Genetic testing must be performed before prescribing or for a subset of patients	Highest level of actionability	HLA-B*5701 for abacavir in all
Testing Recommended	Genetic testing is recommended but not mandatory	Strong clinical relevance	HLA-B*1502 for carbamazepine in Asians
Actionable PGx	Label contains genotype-based dosing, toxicity, efficacy, or contraindication information, but testing is not specifically required or recommended	Clinically actionable	CYP2C19 for Clopidogrel in select
Informative PGx	Genetic information is mentioned but no clinical action is needed	Not clinically actionable	SLCO1B1 for statins

ClinPGx considers the first three categories (Required, Recommended, and Actionable) as clinically relevant pharmacogenomic labels.

Table 3: Current recommendations of pharmacogenomics testing based on FDA and other drug regulatory bodies

Drugs	FDA recommendations	Others (EMA, HCSC)
Abacavir	HLA-B*5701 testing required	HLA-B testing required
Alglucosidase -alfa	GAA testing required	GAA testing required
Afatinib	EGFR testing required	EGFR testing required
Alectinib	ALK testing required	ALK testing required
Arsenic trioxide	PML, RARA testing required	PML, RARA testing required
Azathioprine	NUDT15, TPMT Testing recommended	NUDT15 Testing required TPMT actionable PGx
Capecitabine	ERBB2 (HER2) testing required DPYD testing recommended	DPYD testing recommended
Carbamazepine	HLA-B*1502 testing required	

	HLA-A; actionable PGx	HLA-A*3101; HLA-B*1502; testing recommended
Codeine	CYP2D6; actionable PGx	CYP2D6; actionable PGx
Desflurane/ Isoflurane/ sevoflurane	CACNA1S; RYR1; actionable PGx	CACNA1S; RYR1; actionable PGx
Divalproex sodium	POLG testing required	POLG testing required
Irinotecan or atazanavir	UGT1A1; testing recommended	UGT1A1; actionable PGx
Ivacaftor/ lumacaftor	CFTR; testing required	CFTR; testing required.
Lidocaine/prilocaine	CYP5R3; G6PD; actionable PGx	CYP5R3; G6PD; actionable PGx
Mercaptopurine	NUDT15, TPMT; testing recommended	NUDT15, TPMT; testing recommended
Metoclopramide	CYP2D6; actionable PGx	CYP2D6; actionable PGx
Mivacurium	BCHE; actionable PGx	No label
Neomycin	MT-RNR1; actionable PGx	No label
Oxcarbazepine	HLA-B*15:02; testing recommended	HLA-B*15:02; testing recommended
Pantoprazole	CYP2C19; actionable PGx (children only)	
Pegloticase	G6PD; testing required	G6PD; testing required
Phenytoin	CYP2D9; HLA-B; actionable PGx	HLA-B*15:02; testing recommended
Piroxicam	CYP2D6; actionable PGx	No label
Primaquine	G6PD; testing required	G6PD; testing required
	CYP5R1, 2, 3, and 4; actionable PGx	CYP5R1, 2, 3, and 4; actionable PGx
Rasburicase	G6PD; testing required	G6PD; testing required
Rosuvastatin	SLCO1B1; Informative	ABCG2; SLCO1B1; actionable PGx
Streptomycin	MT-RNR1; actionable PGx	No label
Succinylcholine	BCHE; CACNA1S, RAR1; actionable PGx	BCHE; CACNA1S, RAR1 actionable PGx
Tacrolimus	CYP3A4/5; criteria not met	
Tamoxifen	ESR1, ESR2, PGR; testing required	CYP2D6, actionable PGx
Tamsulosin	CYP2D6; actionable PGx	CYP2D6; informative
Thioguanine	NUDT15, TPMT; Testing recommended	NUDT15, TPMT; testing recommended
Thioridazine	CYP2D6; actionable PGx	No label
Tramadol	CYP2D6; actionable PGx	CYP2D6; actionable PGx
Valbenazine	CYP2D6; actionable PGx	No label
Valproic acid	POLG; testing required	OTC, POLG; actionable PGx
	OTC actionable PGx	CYP2C19; actionable PGx
Vortioxetine	CYP2D6; actionable PGx	CYP2D6; actionable PGx
Voriconazole	CYP2C19; Informative	CYP2C19; actionable PGx
Warfarin	PROC, PROS1; actionable PGx	PROC, PROS1; actionable PGx
	CYP2C9, VKORC1; actionable PGx	CYP2C9, VKORC1; actionable PGx

(Others include EMA, HCSC, DPWG, PMDA, Swiss medic)

Challenges to Clinical Implementation of Pharmacogenomics:

Limited Clinical Evidence for Many Gene–Drug Pairs:

The evidence gap between genetic association and demonstrated clinical utility remains a major obstacle to widespread implementation of pharmacogenomics. Although thousands of pharmacogenomic associations have been reported, only a small proportion have sufficient evidence to support routine clinical use. Most associations are derived from observational studies and lack large randomized controlled trials demonstrating improved patient outcomes.^[18,24]

Cost and Reimbursement Issues:

The perceived upfront cost of pharmacogenomics often outweighs recognition of long-term savings from preventing adverse drug reactions. Economic uncertainty and inadequate reimbursement policies continue to slow the adoption of pharmacogenomic testing.^[25]

Lack of Physician Knowledge and Training:

The principal barrier to pharmacogenomics was not skepticism about genetics but lack of physician education and confidence. Many physicians report limited confidence in interpreting pharmacogenomic test results. Medical curricula often provide insufficient education in genetics, resulting in underuse of available genomic information. The

success of pharmacogenomics depends as much on clinician education as on advances in genomic technology. Stanek et al. demonstrated that while physicians overwhelmingly recognized the importance of genetics in drug response, only a small minority felt adequately trained or routinely used pharmacogenomic testing, identifying education as a critical barrier to clinical implementation.^[26]

Integration into Clinical Workflow:

Even when pharmacogenomic results are available, they are frequently inaccessible at the point of prescribing. Integration into electronic health records and clinical decision support systems remains incomplete in many healthcare settings.^[17]

Population Diversity and Generalizability:

Most pharmacogenomic studies have been conducted in populations of European ancestry. Variant frequencies and drug responses differ substantially among ethnic groups, limiting the applicability of existing recommendations worldwide. Population differences in drug response are often driven by differences in genetic variant frequencies; therefore, pharmacogenomics provides a more precise approach than race-based prescribing.^[27]

Ethical, Legal, and Privacy Concerns

Patients may worry about misuse of genetic information, discrimination, confidentiality breaches, and long-term storage of genomic data. These

concerns can reduce acceptance of pharmacogenomic testing.^[28,29]

Regulatory and Standardization Challenges

Differences between regulatory agencies, laboratories, and guideline developers can create inconsistencies in test interpretation and reporting. Standardization of nomenclature, allele definitions, and reporting formats remains an ongoing challenge.^[30]

Limited Availability in Developing Countries:

Many low- and middle-income countries face challenges of high testing costs, limited laboratory infrastructure, shortage of trained personnel, lack of national guidelines. These barriers widen the gap in access to precision medicine.^[31]

CONCLUSION

"The major future advantage of pharmacogenomics lies not only in improving drug efficacy and safety but also in reducing healthcare costs through preemptive genetic testing and avoidance of adverse drug reactions."

The future of pharmacogenomics is moving beyond single-gene testing toward:

- Multi-gene pharmacogenomic panels
- Whole-genome sequencing
- Polygenic risk scores
- Artificial intelligence-driven prescribing algorithms
- Pharmacogenomics of biologics and immunotherapies
- Gene-editing-based therapeutics

Large-scale initiatives such as the **All of Us Research Program** and the **100,000 Genomes Project** are generating diverse datasets that will enhance the predictive accuracy and equity of pharmacogenomic implementation worldwide.

Pharmacogenomics has evolved from early observations of inherited drug sensitivity to a rapidly advancing discipline at the center of precision medicine. By linking genetic variation to drug efficacy, toxicity, and dosage requirements, pharmacogenomics enables safer, more effective, and individualized therapy. As genomic technologies become increasingly integrated into routine clinical practice, pharmacogenomics is poised to transform prescribing from a population-based approach to truly personalized therapeutics.

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