

THE ROLE OF PHARMACOGENETICS IN PREDICTING DRUG RESPONSE AND ADVERSE DRUG REACTIONS

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Abstract

Give the same dose of the same drug to two patients, and one may be cured while the other is harmed—a problem as old as prescribing itself. Much of that variability is written in the genome. Pharmacogenetics, the study of how inherited variation modifies drug response, has matured from a laboratory curiosity into a clinical discipline with published dosing guidelines for more than a hundred drugs. This narrative review traces the field from its accidental discoveries—haemolysis in G6PD-deficient soldiers given primaquine, prolonged paralysis after suxamethonium, decades of genotype-blind warfarin dosing—to the modern era of international implementation consortia, pre-emptive panel testing, and point-of-care clinical decision support. We review the mechanistic families through which variants act (metabolic enzymes, drug targets, transporters, and immune-related HLA alleles), assemble the landmark gene–drug pairs with proven clinical actionability, and examine the strongest outcome evidence to date: the PREPARE trial, in which a 12-gene panel reduced adverse drug reactions by 25% in nearly seven thousand European patients. We then confront the obstacles—cost, ancestral bias in variant catalogues, drug–drug–gene interactions, education, and ethics—and argue that pharmacogenetics has crossed the threshold from promise to practice. The conclusion is measured but firm: for a growing list of medicines, the most important laboratory test is already inside the patient, waiting to be read once.

Keywords: pharmacogenetics; pharmacogenomics; adverse drug reactions; precision medicine; CYP450; CPIC guidelines; HLA; gene–drug interaction; pre-emptive testing

1. Introduction

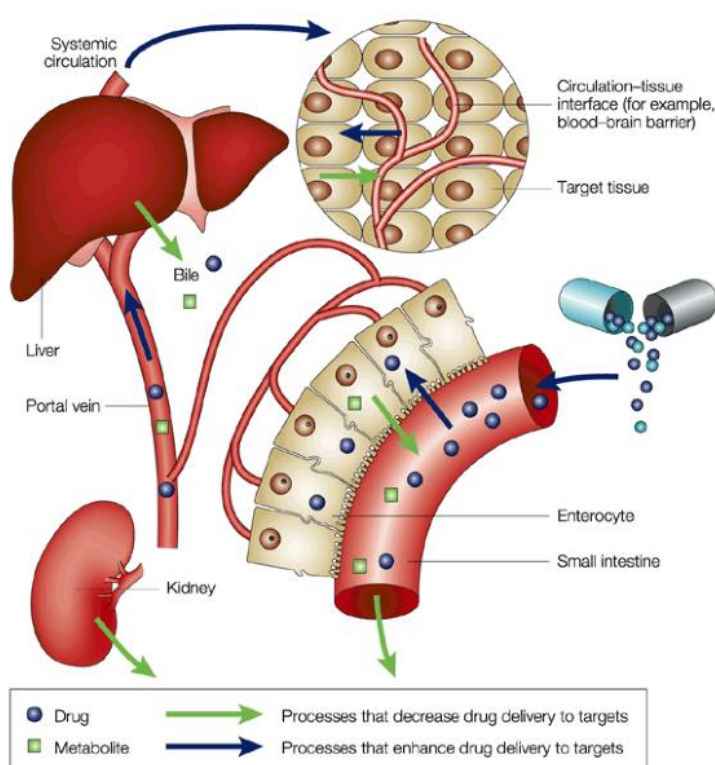
Two patients sit in adjacent beds on a cardiology ward, both having received stents after heart attacks, both started on clopidogrel at the same dose on the same morning. Six months later, one returns to work; the other returns with a stent thrombosis and a second, larger infarction. Nothing about their charts—age, weight, kidney function, smoking—explains the difference. But a single-letter change at position 681 of the CYP2C19 gene does: the patient who carried two loss-of-function alleles converts almost none of the prodrug into its active antiplatelet form and was, in effect, unmedicated during the weeks that mattered most. This is the everyday argument for pharmacogenetics, told not in odds ratios but in a ward round.

The scale of the underlying problem is sobering. Adverse drug reactions remain among the leading causes of hospital admission and in-hospital harm, and large twin and family studies attribute 20% to 95% of the variability in drug response between individuals to heredity—a range that dwarfs what age, organ function, and comorbidity together can explain. For decades, medicine has managed this variability the only way it could: empirically, by starting a standard dose and adjusting by trial, error, and occasionally catastrophe. Pharmacogenetics offers a different sequence—test first, then dose—whose logic has been reinforced by a striking observation: roughly 99% of people carry at least one actionable pharmacogenetic variant somewhere in their genome. This article reviews how that knowledge was discovered, which gene–drug pairs have earned their place in guidelines, what the outcome trials show, and what still stands between the genome and the prescription pad.

2. A Short History of Accidental Discoveries

The field was born of toxicity, not theory. Pythagoras is said to have warned against fava beans, and the haemolytic crises his followers avoided were favism—today understood as acute oxidative destruction of red cells in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The modern era opened in the 1950s, when antimalarial primaquine produced haemolysis in a predictable fraction of soldiers, and when studies of the tuberculosis drug isoniazid revealed two populations—rapid and slow acetylators—whose difference lay in polymorphic N-acetyltransferase. Famously, 6–10% of patients given the muscle relaxant suxamethonium in the 1950s and 1960s suffered prolonged apnoea because of inherited variants in butyrylcholinesterase, a finding that made anaesthetists geneticists by necessity. The molecular watershed came in 1988, when striking ethnic and interindividual differences in the metabolism of the antihypertensive debrisoquine

were traced to the CYP2D6 gene—launching the CYP450 era. The succeeding decades mapped variant after variant: TPMT and mercaptopurine, DPYD and fluorouracil, VKORC1 and warfarin, and a wholly different mechanism in the HLA system, where immune-response alleles presage idiosyncratic hypersensitivity to abacavir and carbamazepine. By the time the Human Genome Project finished, pharmacogenetics had moved from pharmacology footnotes to drug labels, and by 2009 the Clinical Pharmacogenetics Implementation Consortium (CPIC) had formed precisely to solve the next problem—translating genotypes into prescribing decisions.



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Figure 1. The genetic basis of variability in drug response: absorption, distribution, metabolism, and target engagement differ between individuals with different variants, so the same dose delivers very different concentrations and effects. (Reproduced from Nature Reviews Drug Discovery.)

3. How Variants Speak: Four Mechanistic Families

Pharmacogenetic variants act through four recognisable routes. The first and largest is drug metabolism, dominated by the cytochrome P450 superfamily. CYP2D6, CYP2C19, and CYP2C9 are extraordinarily polymorphic—CYP2D6 alone exists as

normal, reduced, absent, and even multi-copy ("ultrarapid") versions—and their combined diplotypes sort patients into poor, intermediate, normal, rapid, and ultrarapid metaboliser phenotypes. The consequences run in both directions: a poor metaboliser given codeine converts almost none of it to morphine and gets no analgesia, while an ultrarapid metaboliser—sometimes carrying three or four active copies—may flood a breastfed infant with morphine from a routine maternal dose, a tragedy documented in case reports and now answered by boxed warnings. Non-CYP enzymes matter too: variants in TPMT and NUDT15 predict thiopurine myelosuppression, and DPYD deficiency converts fluoropyrimidine chemotherapy into life-threatening or lethal toxicity. The second family is pharmacodynamic: VKORC1 variants change warfarin's target itself, explaining much of the dose gap between a patient needing 2 mg and one needing 10 mg daily. The third is transport: SLCO1B1 variants impair hepatic statin uptake and raise simvastatin-associated myopathy risk sharply in carriers of two risk alleles. The fourth, and most dramatic, is immune: specific HLA alleles act as molecular gatekeepers of severe hypersensitivity—HLA-B*57:01 for abacavir, HLA-B*15:02 for carbamazepine-induced Stevens–Johnson syndrome in South-East Asian populations, and HLA-B*58:01 for allopurinol hypersensitivity. For these, the test is not about dose but about veto: carrying the allele contraindicates the drug outright.

Gene–drug pair		Variant effect	Clinical action	Comments
CYP2C19 clopidogrel	–	Loss-of-function alleles impair prodrug activation	Avoid clopidogrel in poor metabolisers; use prasugrel/ticagrelor	Boxed warning; ~30% of patients have suboptimal response
CYP2C9 VKORC1 warfarin	/ –	Reduced clearance; increased target sensitivity	Lower starting dose per FDA label/CPIC algorithm	Genotype explains a large share of dose variability; label updated 2007/2010
HLA-B*57:01 abacavir	–	Immune-mediated hypersensitivity	Test before prescribing; drug contraindicated if positive	Testing made routine; virtually eliminated abacavir hypersensitivity reactions

HLA-B*15:02 – carbamazepine	Stevens–Johnson syndrome / toxic epidermal necrolysis	Test at-risk ancestries (e.g., South-East Asian); avoid if positive	Prevalence of allele drives regional testing policy
HLA-B*58:01 – allopurinol	Severe cutaneous adverse reactions	Test before therapy in high-risk groups; avoid if positive	Strongest HLA association known; relevant to gout therapy worldwide
CYP2D6 – codeine, tramadol, tamoxifen	Ultra-rapid: toxicity (respiratory depression); poor: no efficacy	Avoid in ultra-rapid metabolisers; alternative analgesics; tamoxifen adjuvant choice	Breastfeeding infant deaths prompted boxed warnings
TPMT / NUDT15 – azathioprine, mercaptopurine	Thiopurine over-exposure → myelosuppression	Start at greatly reduced dose or avoid	Standard pre-treatment test in gastroenterology, oncology, transplant
DPYD – 5-fluorouracil, capecitabine	DPD deficiency → severe/life-threatening toxicity	Dose reduction per activity score or avoid	CPIC guideline; prevents avoidable chemotherapy deaths
SLCO1B1 – simvastatin	Impaired hepatic uptake → myopathy risk	Limit dose or choose alternative statin	CPIC guideline for statin-associated muscle symptoms
G6PD – rasburicase, primaquine	Oxidative haemolysis risk	Avoid in deficient patients; test per label	Old example, still required by FDA label

Table 1. Landmark gene–drug pairs with established clinical actionability.

4. The Trial Evidence: From Association to Outcomes

For years the field's critics offered a fair challenge: pharmacogenetics had mechanism and guidelines, but where were the randomised outcome data? That gap has now been substantially closed. The strongest result comes from the PREPARE study, an open-label, multicentre, cluster-randomised crossover implementation trial published in *The Lancet*: 6,944 patients across seven European countries were tested with a 12-gene pharmacogenetic panel, and treating physicians received the results with guideline-based recommendations. Adverse drug reactions occurred in 21.5% of the genotype-guided arm versus 28.6% with standard treatment—a 25% relative reduction, with an odds ratio of 0.70. Supporting data are consistent across settings: HLA-B*57:01 screening essentially eliminated immunologically confirmed abacavir hypersensitivity; genotype-guided warfarin dosing using validated algorithms outperformed clinical-only dosing in the early, highest-risk weeks in several trials; and DPYD-guided fluoropyrimidine dosing has become an oncology safety standard. Cumulatively, the evidence has shifted the question from "does pharmacogenetic testing work?" to "how do we make it routine?"

5. From Bench to Bedside: Guidelines, Panels, and Decision Support

The translational engine of the field is the guideline ecosystem. CPIC publishes freely available, peer-reviewed, regularly updated gene–drug guidelines with standardised phenotype terminology and activity scores; the Dutch Pharmacogenetics Working Group and national networks contribute parallel guidance; and the Pharmacogenomics Knowledgebase (PharmGKB) curates the evidence that feeds them. As of recent tallies, genotype-based recommendations exist for well over a hundred drugs across roughly two dozen genes—CPIC alone covers 79 drugs—yet the number of genes is modest precisely because a handful of enzymes metabolise so many medicines. The FDA, for its part, maintains a table of pharmacogenetic associations in drug labels, ranging from outright requirements (abacavir, rasburicase) to actionable dosing information (warfarin, clopidogrel) to descriptive mentions of uncertain utility.

Two implementation models compete. Reactive testing orders a single-gene test when a particular drug is prescribed—the traditional approach, simple but perpetually one step behind, since results arrive after decisions. Pre-emptive panel testing genotypes a panel of core pharmacogenes once, stores the result in the electronic health record, and fires an alert whenever a future prescription hits a stored variant—turning a lifetime of encounters into opportunities. Health systems that have built this infrastructure, from children's hospitals to academic medical centres, report workflows in which the

prescription, the genotype, and the guideline meet at the exact moment of decision, as depicted in Figure 2. The cost logic favours panels: with ~99% of individuals carrying at least one actionable variant and dozens of high-use drugs affected, a single test amortises across decades of prescribing.

Dose and Medicine Selection Based On Genomic Profile

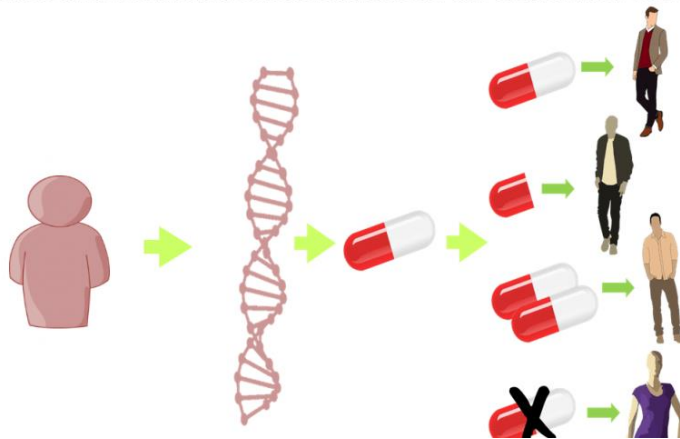


Figure 2. Dose and medicine selection based on genomic profile: the same drug yields benefit, reduced benefit, or harm depending on the patient's variants—one reason pre-emptive panel testing is replacing reactive single-gene testing. (Image: ZibdyHealth.)

Phenotype	Typical diplotype/activity	General prescribing implication
Poor metaboliser	Two no-function alleles (activity score 0)	Greatly reduced metabolism: risk of toxicity at standard doses or no efficacy for prodrugs (clopidogrel). Reduce dose, avoid, or choose alternative.
Intermediate metaboliser	One normal + one no-function allele (score 0.5–1.25; gene-specific)	Moderately reduced metabolism: dose reduction may be recommended for high-risk drugs; monitor closely.
Normal metaboliser	Two normal-function alleles	Standard dosing anticipated; no adjustment.

Rapid metaboliser	Increased-function allele(s) with normal function (score >2)	Increased metabolism: higher dose may be needed for some drugs; watch for subtherapeutic exposure.
Ultrarapid metaboliser	Multi-copy or strong increased-function alleles	Markedly increased metabolism: prodrugs (codeine) can cause severe toxicity—avoid; some substrates may need dose escalation or alternatives.
Indeterminate unknown /	Uncharacterised alleles or ambiguous diplotype	Treat as normal metaboliser unless clinical factors suggest otherwise; avoid assuming altered phenotype without evidence.

Table 2. CPIC standardised metaboliser phenotype terminology (CYP450 genes) and its general prescribing logic.

6. What Still Stands in the Way

Honesty requires the obstacles to be named as clearly as the successes. Cost and reimbursement lag behind evidence in many systems, leaving patients to fund tests that guidelines already justify. Variant catalogues carry an ancestral skew: most pharmacogenetic data derive from European-ancestry cohorts, so allele frequencies—and therefore testing yield and accuracy—differ across populations, a scientific and equity problem the field is only beginning to repair through diverse biobanking. Drug–drug–gene interactions are under-served by current tools, which typically address a drug pair or a gene–drug pair, rarely both: a CYP2D6 inhibitor can phenoconvert a normal metaboliser into a functional poor one, and guidelines are only now catching up with combination logic. Education remains a bottleneck—surveys repeatedly show prescribers undertrained and underconfident—and laboratory reporting formats still vary. Ethically, the field must resist overreach: incidental findings, insurance

implications, and the temptation to stretch beyond evidence all demand restraint. None of these obstacles is fundamental; all are administrative, curricular, or scientific, and each is being actively worked on.

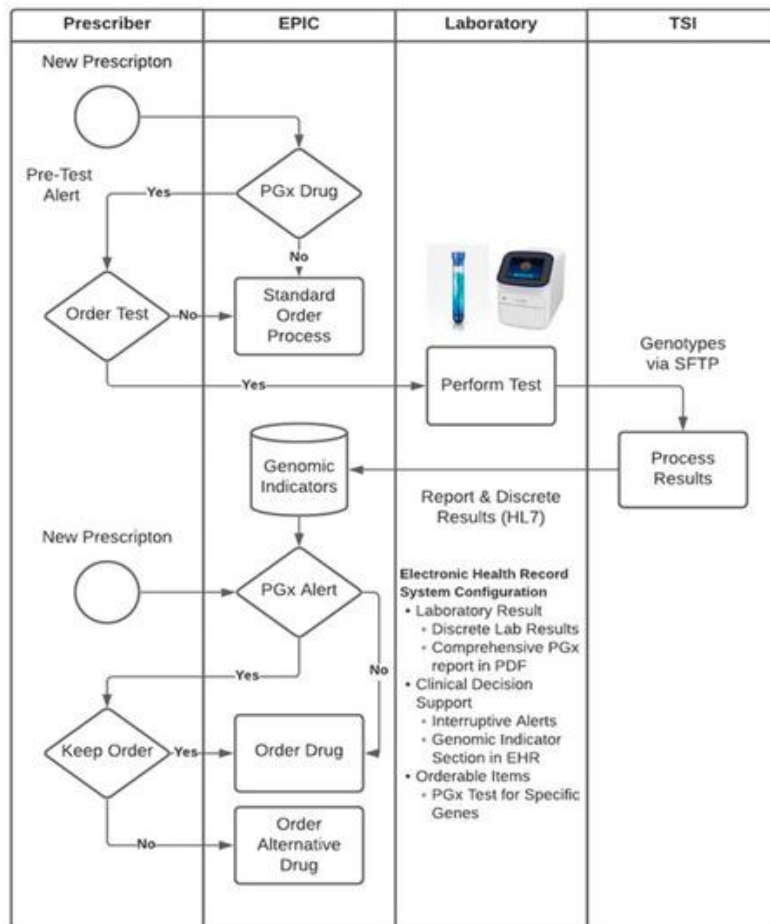


Figure 3. Real-world implementation of pharmacogenomics: a single-centre workflow in which new prescriptions trigger pre-test alerts, panel testing, and genotype-guided decision support at the point of ordering. (Adapted from Arkansas Children's Hospital experience, JPM.)

7. Conclusion

The ward vignette with which this article opened no longer needs to end with a second heart attack. The variant that silently defeated clopidogrel is detectable with a test whose marginal cost falls every year; the guideline translating that result into an alternative drug exists, is free, and is updated as evidence matures; and the trial proof—25% fewer adverse drug reactions across nearly seven thousand patients—has been published in one of medicine's most demanding journals. What remains is adoption: embedding genotypes in health records, wiring alerts into prescribing, paying for the

test once instead of paying for the reaction repeatedly, and teaching the next generation of clinicians to read the genome as naturally as they read a creatinine. Pharmacogenetics does not promise perfect prediction—drug response is multifactorial, and environment, adherence, and drug–drug interactions will always share the stage. But for a defined and growing list of medicines, it has already done something medicine rarely achieves: it has converted a portion of clinical uncertainty into a letter of the alphabet, read once, acted upon, and carried by the patient for life. The most rational next step in therapeutics is to start reading it before the first dose, not after the first disaster.

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