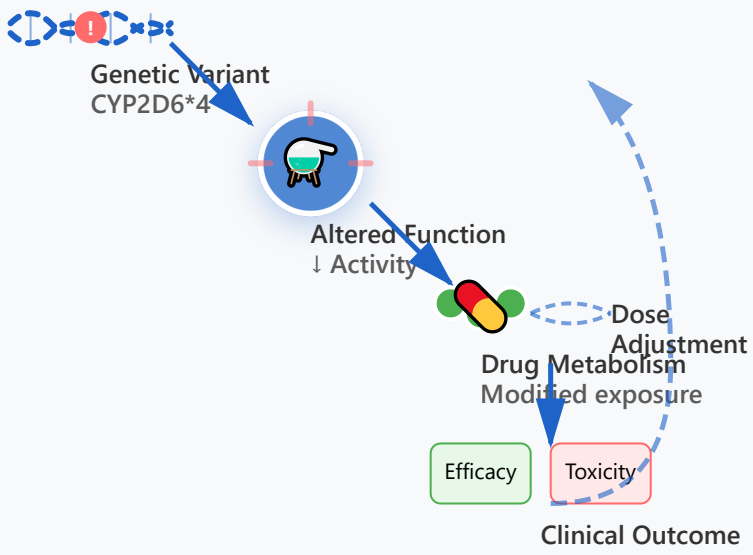
Pharmacogenomics (PGx)



PGx Variants

Genetic variations affecting drug response, metabolism, and efficacy

Drug Metabolism

CYP450 enzymes and transporter polymorphisms impact drug levels

Dosing Algorithms

Genotype-guided dosing for warfarin, clopidogrel, and more

CPIC Guidelines

Clinical Pharmacogenetics Implementation Consortium standards

Implementation Barriers: Cost, infrastructure, education, and workflow integration remain challenges for widespread PGx adoption

1 Pharmacogenomic Variants

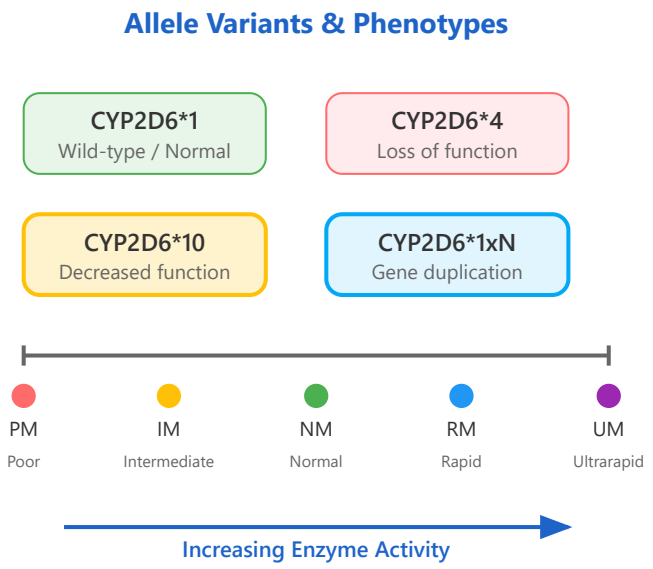
Pharmacogenomic variants are genetic differences that influence how individuals respond to medications. These variations can occur in genes encoding drug-metabolizing enzymes, drug transporters, drug targets, or genes involved in immunological responses.

Key Concepts:

- **SNPs (Single Nucleotide Polymorphisms):** Most common type of genetic variation
- **Star Alleles (*):** Nomenclature system for categorizing variant combinations
- **Copy Number Variations:** Gene duplications or deletions affecting enzyme expression
- **Phenotype Prediction:** Variants determine metabolizer status (PM, IM, NM, RM, UM)
- **Ethnic Differences:** Variant frequencies vary significantly across populations

Clinical Example: CYP2C19

A patient with CYP2C19*2/*2 genotype (poor metabolizer) cannot effectively convert clopidogrel to its active form, increasing risk of cardiovascular events. Alternative antiplatelet therapy should be considered.



2 Drug Metabolism & Enzyme Polymorphisms

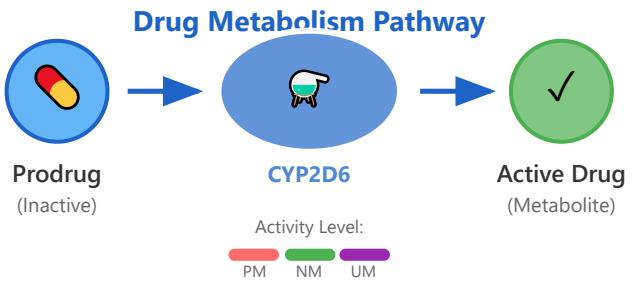
The cytochrome P450 (CYP) enzyme family is responsible for metabolizing approximately 75% of all drugs. Genetic polymorphisms in CYP genes can significantly alter enzyme activity, leading to altered drug plasma concentrations and clinical effects. Transporters also play crucial roles in drug absorption, distribution, and elimination.

Major Drug-Metabolizing Enzymes:

- **CYP2D6:** Metabolizes antidepressants, antipsychotics, beta-blockers, opioids
- **CYP2C19:** Processes PPIs, clopidogrel, some antidepressants
- **CYP2C9:** Metabolizes warfarin, NSAIDs, phenytoin
- **CYP3A4/5:** Most abundant, metabolizes >50% of drugs
- **Transporters (SLCO1B1, ABCB1):** Affect drug uptake and efflux

Clinical Example: Codeine Metabolism

CYP2D6 converts codeine to morphine (active form). Poor metabolizers get minimal pain relief, while ultrarapid metabolizers risk morphine toxicity. This is particularly dangerous in children and breastfeeding mothers.



Clinical Outcomes:

Poor Metabolizer (PM): ↓ Active drug → Reduced efficacy

Normal Metabolizer (NM): Normal drug levels

Ultrarapid Metabolizer (UM): ↑ Active drug → Risk of toxicity

3 Genotype-Guided Dosing Algorithms

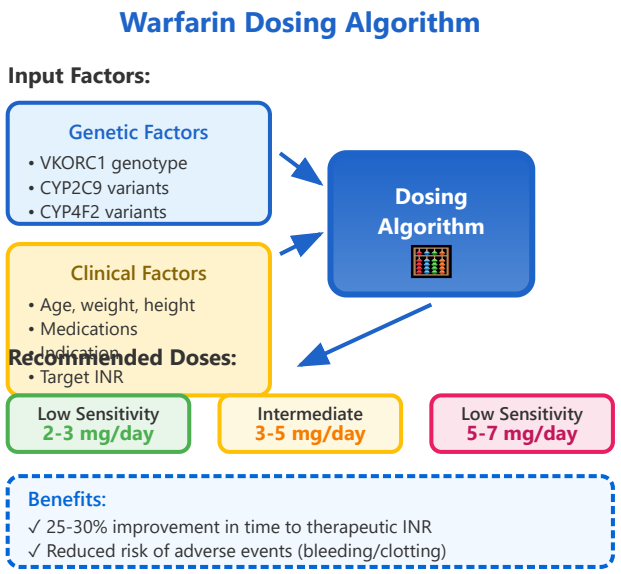
Pharmacogenomic-guided dosing algorithms integrate genetic information with clinical factors to optimize drug dosing. These algorithms have been validated for several high-risk medications and are increasingly being implemented in clinical practice to improve efficacy and reduce adverse events.

Key Dosing Applications:

- **Warfarin:** VKORC1 and CYP2C9 variants guide initial dosing (30-40% dose variation)
- **Clopidogrel:** CYP2C19 LOF alleles indicate need for alternative agents
- **Thiopurines:** TPMT and NUDT15 variants prevent severe myelosuppression
- **Fluoropyrimidines:** DPYD variants reduce 5-FU/capecitabine toxicity risk
- **Tacrolimus:** CYP3A5 genotype optimizes immunosuppression dosing

Clinical Example: Warfarin Dosing

Patient with VKORC1 -1639 AA and CYP2C9 *1/*3 genotypes requires ~30% lower warfarin dose than wild-type patients. Genotype-guided dosing reduces time to therapeutic INR and bleeding events.



4 CPIC Guidelines & Implementation

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides peer-reviewed, evidence-based guidelines for translating genetic test results into actionable prescribing decisions. These guidelines are freely available and regularly updated to reflect current evidence.

CPIC Framework:

- **Level A:** Strong recommendation - preponderance of evidence supports action
- **Level B:** Moderate recommendation - evidence supports action
- **Level C:** Optional - evidence is weak/conflicting
- **Level D:** No recommendation - insufficient or no evidence
- **Gene-Drug Pairs:** >460 guidelines covering 24 genes and 100+ drugs

Clinical Example: HLA-B*57:01 & Abacavir

CPIC Level A recommendation: DO NOT prescribe abacavir to patients positive for HLA-B*57:01 due to nearly 100% risk of severe hypersensitivity reaction. Pre-emptive testing is standard of care.