

Introduction to Pharmacogenomics

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The study of how an individual's genetic makeup influences their response to drugs.

1. What Is Pharmacogenomics?

Term	Definition
Pharmacogenomics	Integration of pharmacology (the study of drug action) and genomics (the study of the genome) to predict drug efficacy and safety based on genetic variation.
Pharmacogenetics	Often used interchangeably, but technically refers to the effect of a single gene on drug response, whereas pharmacogenomics looks at the whole genome.
Precision Medicine	Clinical approach that uses pharmacogenomic data (among other biomarkers) to tailor therapy to each patient.

2. Why It Matters

1. **Improved Efficacy** – Matching drugs to patients who are most likely to benefit.
 2. **Reduced Adverse Drug Reactions (ADRs)** – Identifying carriers of risk alleles that predispose to toxicity.
 3. **Optimized Dosing** – Adjusting dose based on metabolic capacity (e.g., poor vs. ultra-rapid metabolizers).
 4. **Cost-Effectiveness** – Preventing trial-and-error prescribing and costly hospitalizations.
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3. Core Concepts

Concept	Explanation	Example
Genetic Polymorphism	Variation in DNA sequence among individuals (e.g., SNPs, insertions, deletions).	<i>CYP2C19</i> *2 allele ? reduced activation of clopidogrel.
Drug-Metabolizing Enzymes	Proteins that biotransform drugs (Phase I – oxidation/reduction; Phase II – conjugation).	<i>CYP450</i> family, <i>UGT1A1</i> .

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Drug Targets	Genes encoding receptors, enzymes, transporters that drugs bind to.	<i>VKORC1</i> variants ? warfarin sensitivity.
Transporters	Proteins that move drugs across membranes, influencing absorption and elimination.	<i>SLCO1B1</i> variants ? statin-induced myopathy.
Gene-Drug Interaction	The functional consequence of a genotype on a drug's pharmacokinetics (PK) or pharmacodynamics (PD).	<i>TPMT</i> deficiency ? thiopurine toxicity.

4. Major Gene Families Involved

Gene Family	Primary Role	Clinically Relevant Drugs
CYP450 (e.g., <i>CYP2D6</i> , <i>CYP2C9</i> , <i>CYP2C19</i>)	Phase I metabolism (oxidation)	Codeine, warfarin, clopidogrel, antidepressants
UGT (UDP-glucuronosyltransferases)	Phase II metabolism (glucuronidation)	Irinotecan, lamotrigine
DPD (DPYD)	Catabolism of fluoropyrimidines	5-Fluorouracil, capecitabine
TPMT, NUDT15	Inactivation of thiopurines	Azathioprine, 6-mercaptopurine
SLCO1B1	Hepatic uptake transporter	Simvastatin, rosuvastatin
VKORC1	Vitamin K epoxide reductase (warfarin target)	Warfarin
HLA (e.g., <i>HLA-B*57:01</i>)	Immune presentation, drug hypersensitivity	Abacavir