Genomic and Precision Medicine

Week 6: Clinical applications of genomics — Pharmacogenomics

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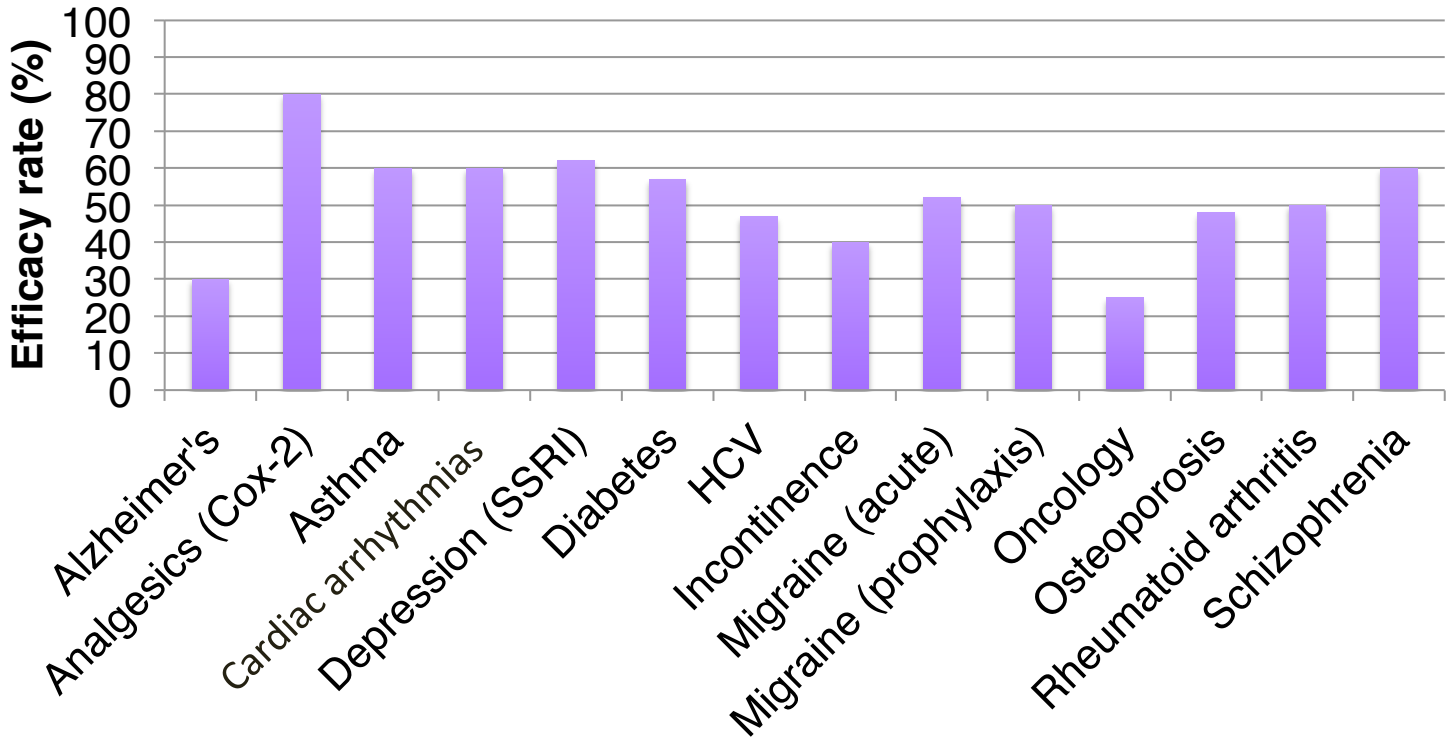
The Lecture

- **MODULE 1**: Background
  - Genetic factors influence pharmacokinetics
  - Genetic factors influencing pharmacodynamics
- **MODULE 2**: What pharmacogenomic tests are available?
- **MODULE 3**: Is my patient a candidate for pharmacogenomic testing?
- **MODULE 4**: Where to get testing done and how to interpret the results

MODULE 1: Background — Genetic factors affecting pharmacokinetics and pharmacodynamics

Drug Efficacy

- Drug response rates range from ~25-80%
- Characterized by inter-individual variability



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Adapted from: Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med 2001; 7:201–204.

Adverse Drug Reactions

Table 1. Commonly Identified Drugs in Adverse Drug Reaction Studies

Therapeutic Category With Drug Class	Drug
Cardiovascular	
β-Blockers	Atenolol, metoprolol
Angiotensin-converting enzyme inhibitors	Lisinopril
Diuretics	Furosemide, hydrochlorothiazide
Calcium channel blocker	Diltiazem, verapamil
Inotropic agents/pressors	Digoxin
Analgesic	
Nonsteroidal anti-inflammatory drugs	Aspirin, piroxicam, ibuprofen, naproxen
Psychiatric	
Tricyclic antidepressants	Imipramine hydrochloride, nortriptyline hydrochloride
Selective serotonin reuptake inhibitor	Fluoxetine
Antibiotics	
Penicillin	Amoxicillin
Antitubercular agents	Isoniazid, rifampin
Macrolides	Erythromycin
Other	
Anticoagulants	Warfarin sodium
Corticosteroids	Prednisone
Anticonvulsants	Carbamazepine, phenytoin
Antidiabetic agents	Insulin
Bronchodilators	Theophylline
Electrolytes	Potassium
Antiemetic or antihistamine	Meclizine hydrochloride

	Incidence of ADRs
Outpatients	2% (1.2-3.2%)
Inpatients	1.6% (0.1-51%)

- ADR: unintented and noxious
- ADRs, although individually rare, are collectively common

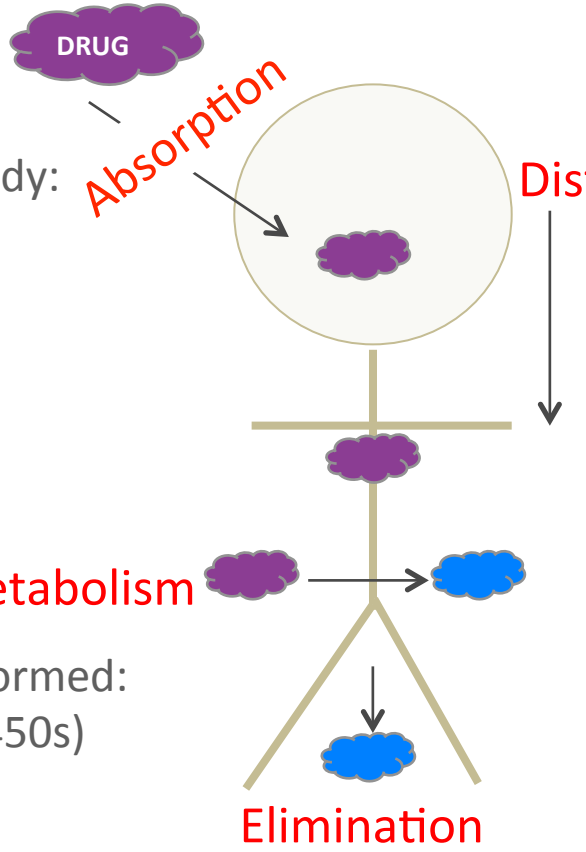
(Hakkarainen KM, et. al. PLoS ONE, 2012;7(3):e33236)

Pharmacogenomics

- Using a patient's genomic information to improve the efficacy and/or reduce the side effects of drugs

Pharmacokinetics

- How the drug concentration changes as it moves through the body



How drug gets into body:
- Orally
- Intravenously
- Inhaled

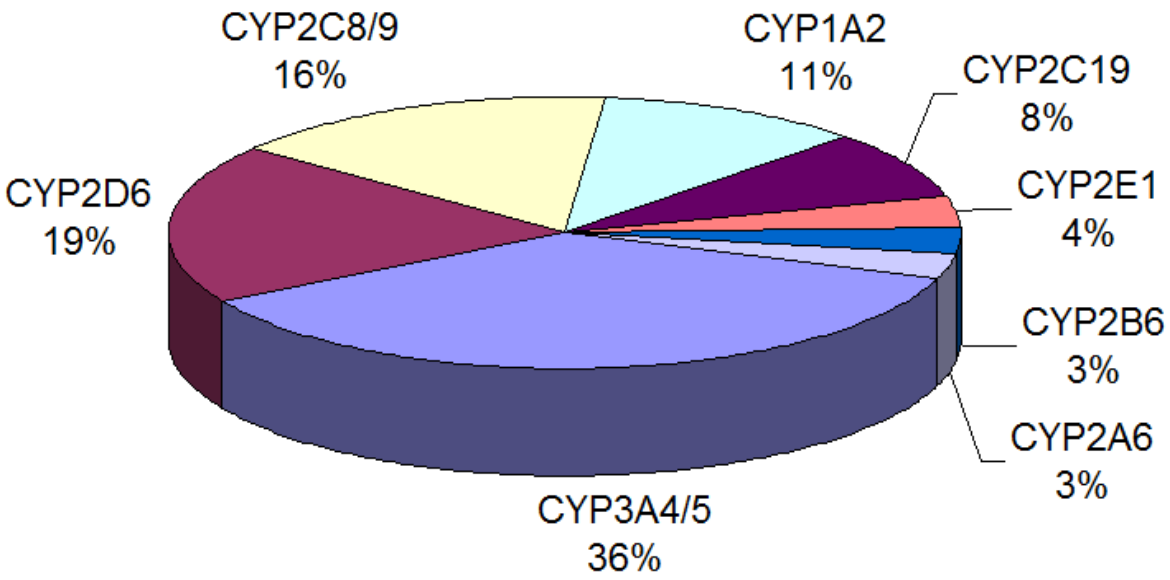
How drug gets into tissues and fluids:
- Circulatory system
- Transporters (e.g. SLCO1B1)

How drug is biotransformed:
- Enzymes (e.g. CYP450s)

How drug is excreted from body:
- Urine (renal/kidney)
- Feces
- Breath

Many drugs are metabolized by the polymorphic Cytochrome P450 enzymes

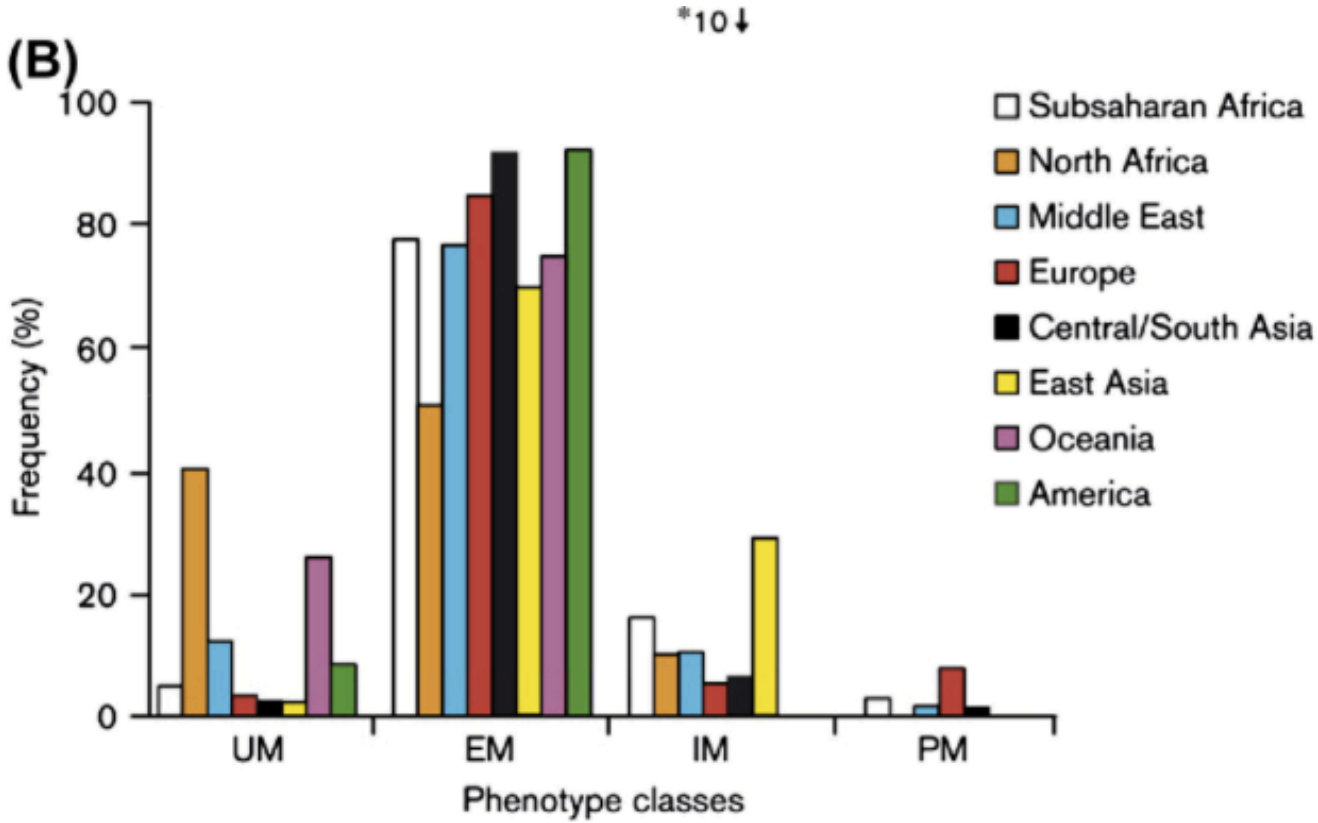
Proportion of all drugs metabolized by different CYP450s



	Enzyme activity
UM	Ultrarapid metabolizer
EM	Extensive (normal) metabolizer
IM	Intermediate metabolizer
PM	Poor metabolizer

Variable activity of CYP2D6 by ethnicity

Activity of CYP450 enzymes varies by race



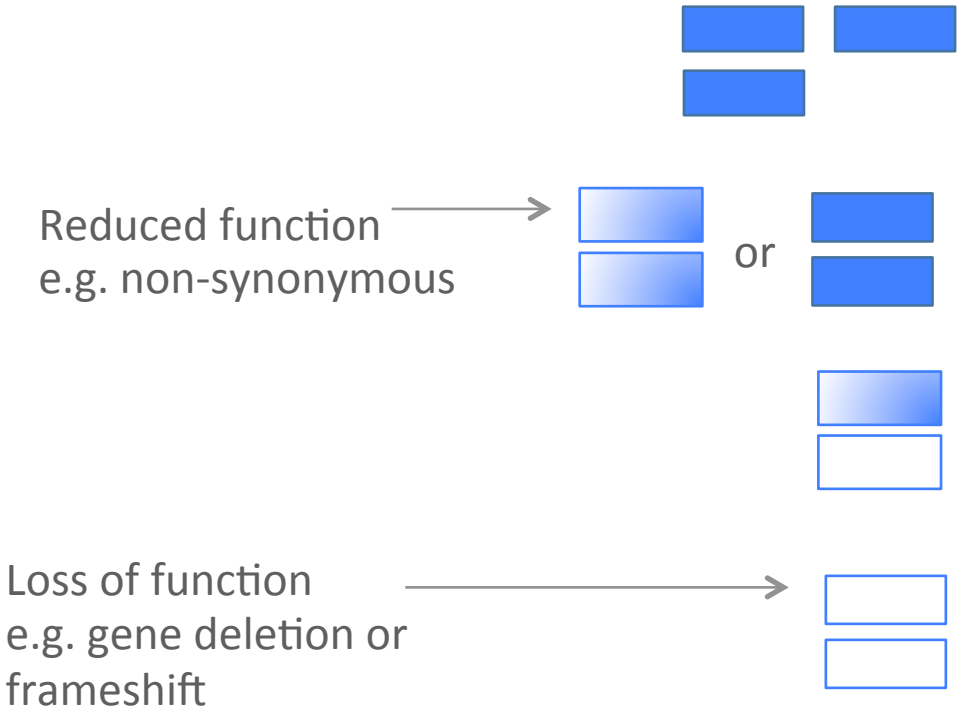
PMs are mainly found in European populations

UMs are mainly found in North Africa

Sistonen J et al. Pharmacogenet Genomics. 2007 Feb;17(2):93-101.

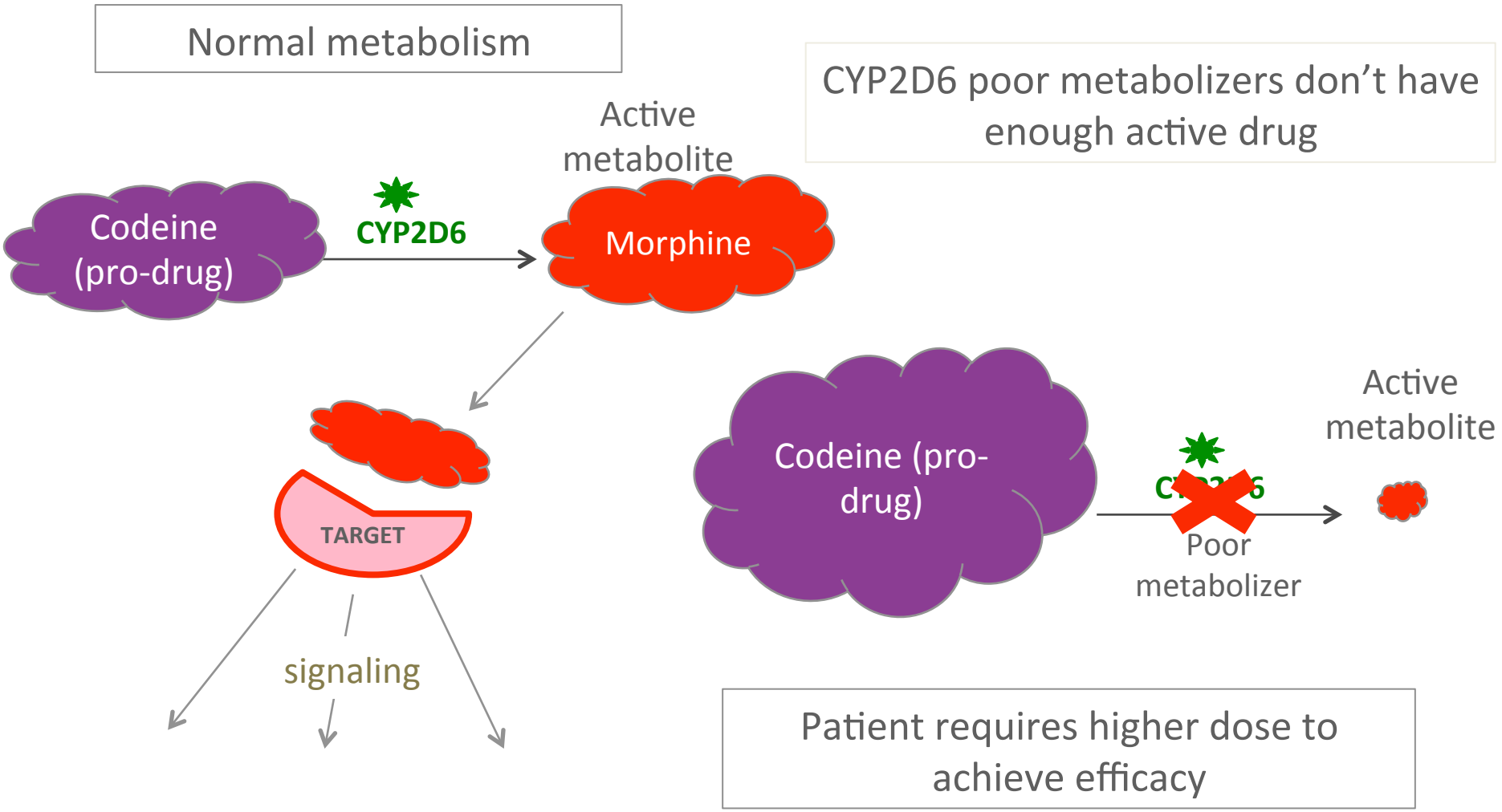
Polymorphic effect of CYP2D6 variants

Dozens of genetic variants can lead to reduced or complete loss of gene function



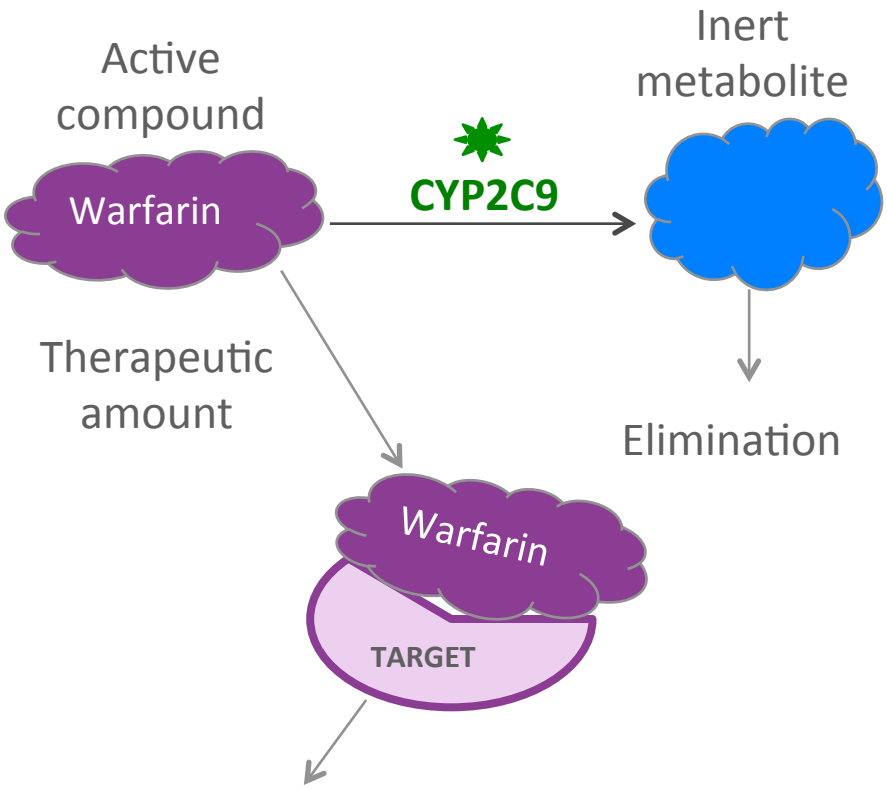
	Underlying genetics
UM	Extra copy(s) of gene
EM	Normal functioning genes (most people)
IM	One non-functioning and one reduced functioning allele
PM	Two non-functioning alleles

Pharmacogenomics — Codeine metabolism

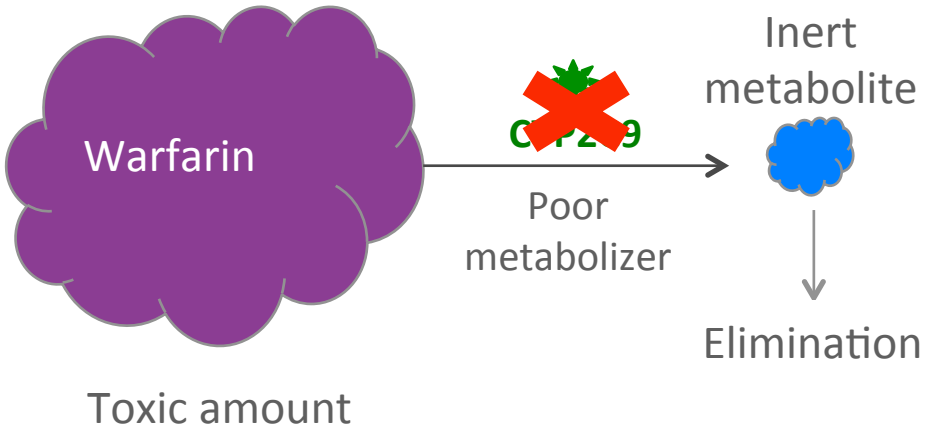


Pharmacogenomics — Warfarin metabolism

Normal metabolism



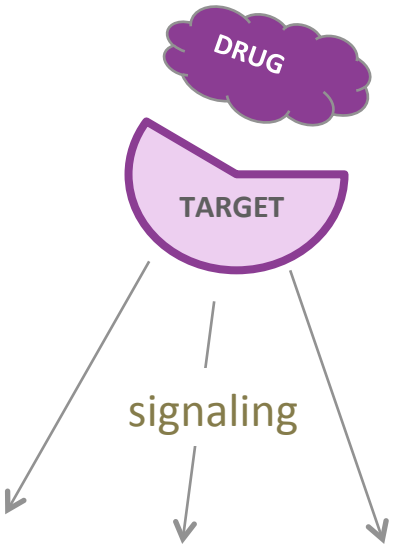
CYP2C9 poor metabolizers have too much drug (toxicity)

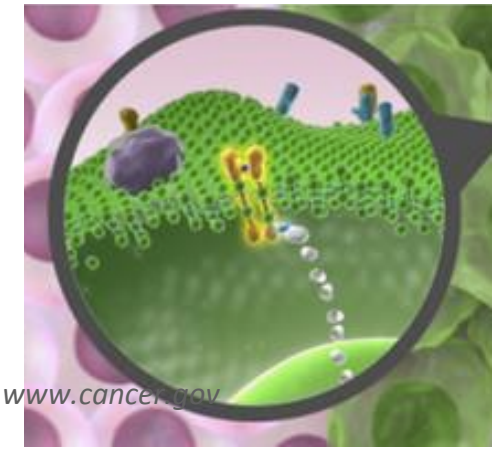


Patient requires lower dose to prevent toxic side effects

Pharmacodynamics

How the drug exerts its effect on the body (potency)



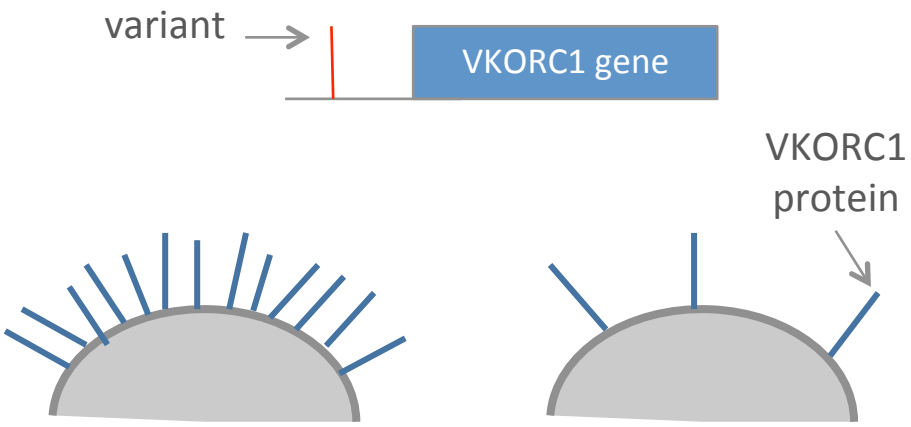


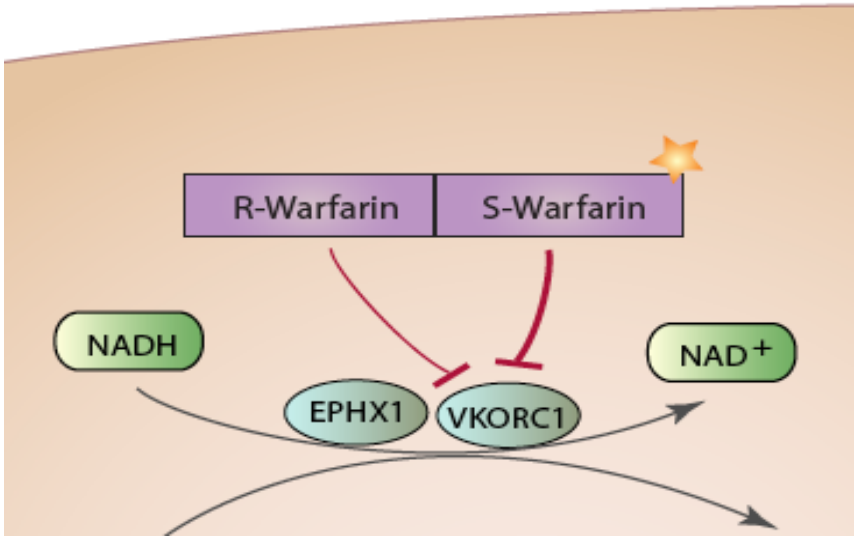
www.cancer.gov

Pharmacodynamics — Warfarin target

VKORC1, target of courmarin derivatives (e.g. Warfarin)

Variant upstream of VKORC1 leads to reduced expression





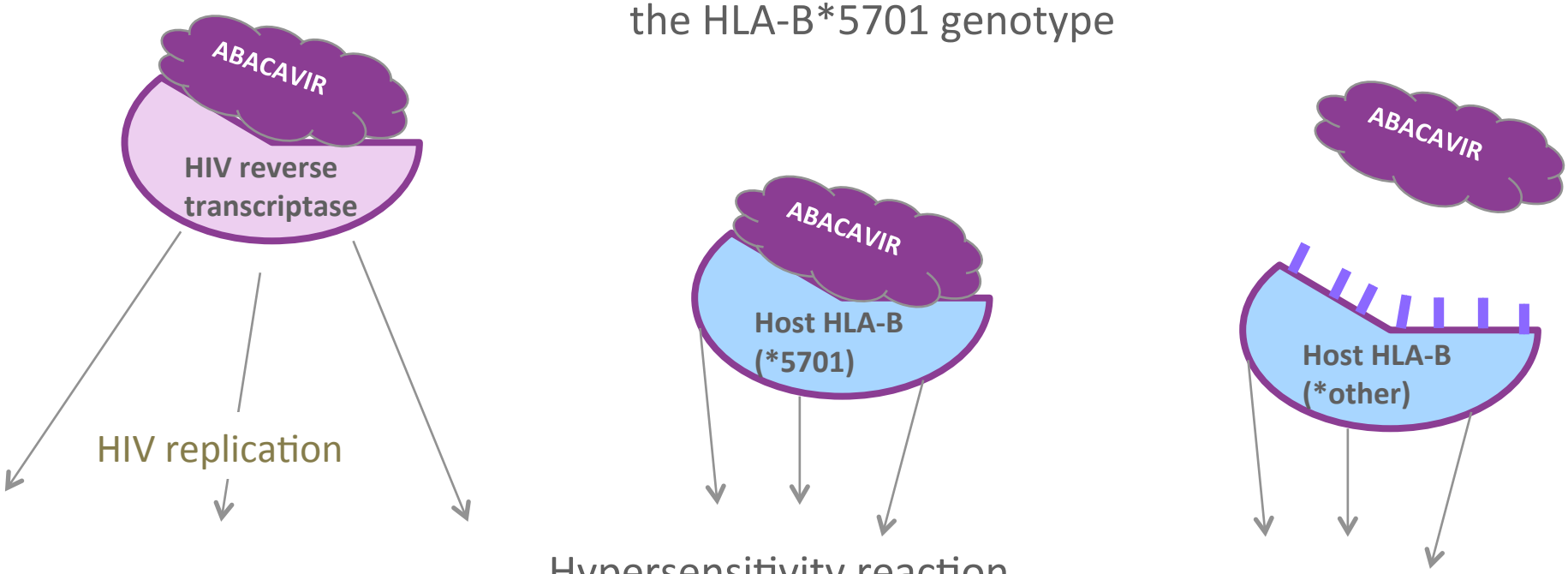
https://www.pharmgkb.org/pathway/PA145011114

More sensitive to inhibition by Warfarin; lower dose required

Off target effects — Abacavir hypersensitivity

Drug affects target, but also interacts with unintended target

Abacavir binds to host HLA-B in patients with the HLA-B*5701 genotype



Hypersensitivity reaction, potentially life-threatening

Patients should avoid drug

No reaction

Patient is fine

Question

Genetic variation in cytochrome P450 genes can impact a drug's:

A. Efficacy
B. Toxicity
C. Both

Answer

C. BOTH

We saw examples of CYP450 polymorphisms affecting efficacy (codeine) and toxicity (warfarin)