

Pharmacogenetics of CYP-mediated drug metabolism

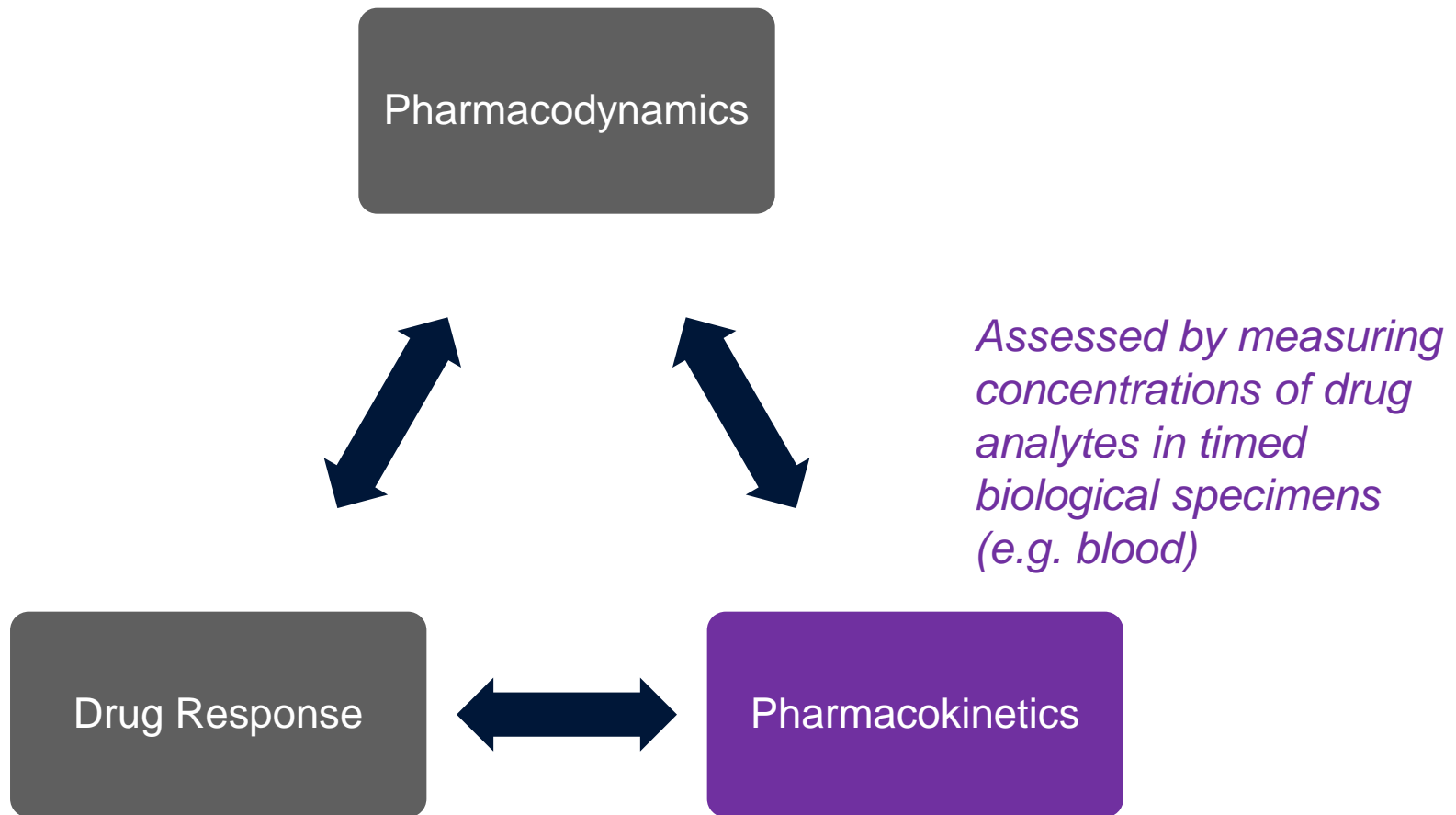
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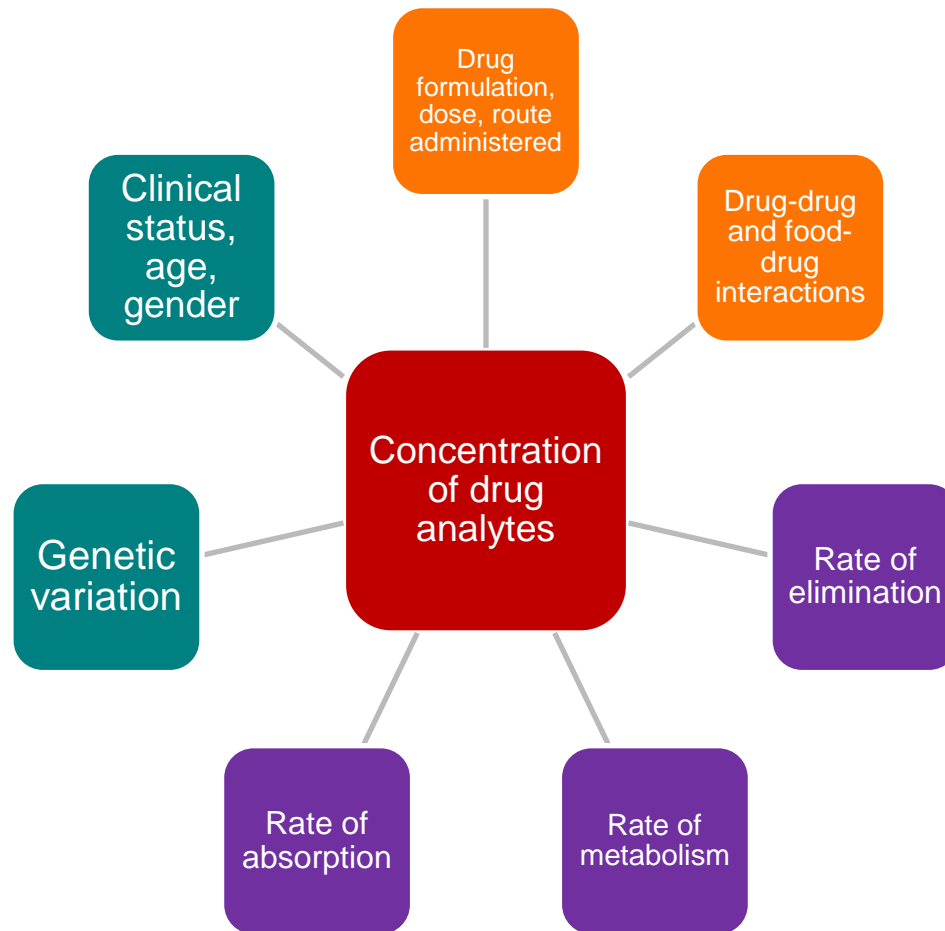
Objectives

- Describe the role of drug metabolism in the activation and inactivation of drugs
- Explain the nomenclature of cytochrome P450 enzyme phenotypes and genetic variants
- List examples of CYPs and drugs with pharmacogenetic associations, and how they would be used to guide drug and dose selection

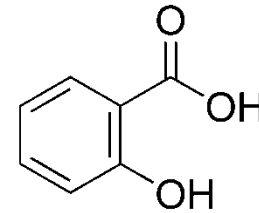
Drug response reflects both pharmacokinetic and pharmacodynamic processes



Factors that affect the concentration of drug analytes in the blood



Drug metabolism



- Metabolism = biochemical modification, usually mediated by specialized enzymes
 - **Phase I reactions:** oxidation, reduction, hydrolysis
(e.g. CYP2C9, CYP2C19, CYP2D6, DPYD)
 - **Phase II reactions:** conjugation (e.g. UGT1A6, TPMT)
- Phase I and II reactions may occur independently or in sequence
- Reaction products usually have different pharmacological activity or potency than the parent drug

Cytochrome P450 (CYP) nomenclature

Gene/enzyme
name

“Star” allele
name

CYP2D6*4E

100C>T
1661G>C
1846G>A
4180G>C

Family

Subfamily

Polypeptide

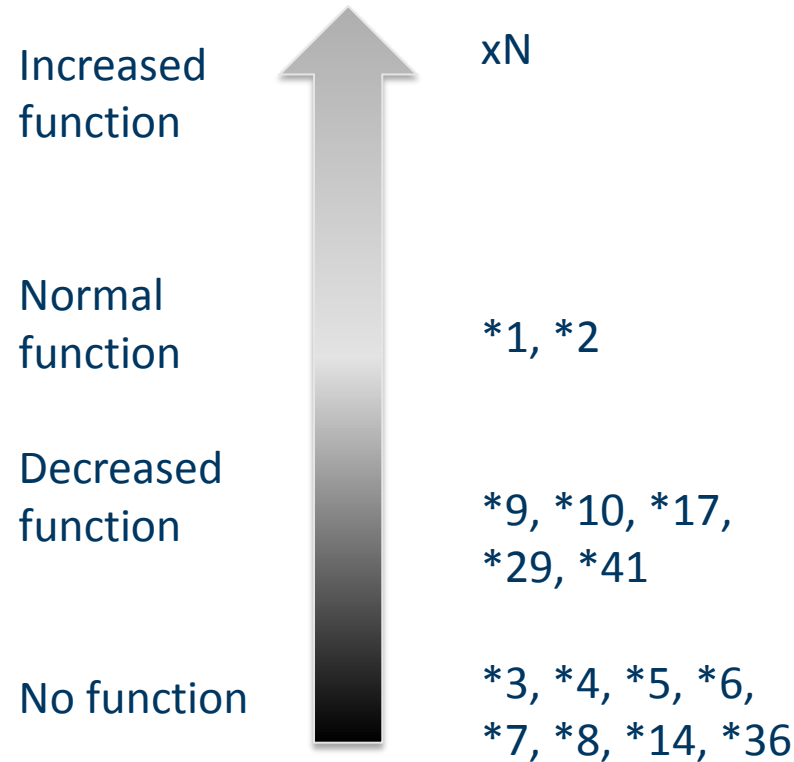
Allele subtype

Allele

**1 suggests that no variants were detected*

<http://www.cypalleles.ki.se/>

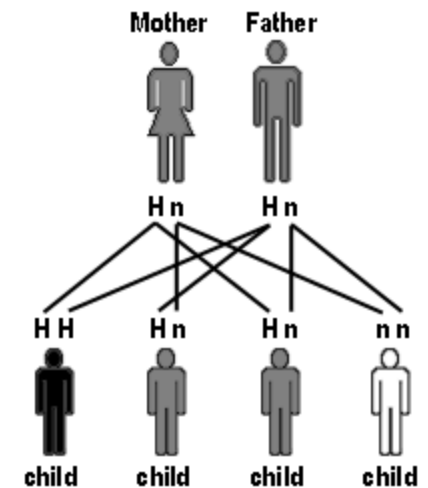
Functional status of common *CYP2D6* alleles



<http://www.cypalleles.ki.se/>

Genetic variation in drug metabolizing enzymes is used to predict the metabolic phenotype

Allele 1	Allele 2	Gene duplication	Phenotype
Normal function	Normal function	Yes	Ultra-rapid metabolizer
Normal function	Increased function	No	Rapid metabolizer
Normal function	Normal function	No	Normal metabolizer
No function	Decreased function	No	Intermediate metabolizer
No function	No function	No/Yes	Poor metabolizer



Caudle et al, *Genetics in Medicine*, 2016

Genetic variation in drug metabolizing enzymes is also used to predict the CYP2D6 activity score

Allele functional status	Allele activity score
Normal function	1
Decreased function	0.5
No function	0

The CYP2D6 activity score is a quantitative value based on the sum of the allele activity scores

$$(\text{Allele 1 Score}) + (\text{Allele 2 Score}) = \text{Total Score}$$

Range of CYP2D6 activity scores based on diplotype (combinations of alleles)

Phenotype	Diplotype (combinations of alleles)	Activity score
Ultra-rapid metabolizer	2 normal function alleles + gene duplication	>2
Normal metabolizer	2 normal function alleles	2
	1 normal function + 1 decreased function alleles	1.5
	1 normal function + 1 no function alleles	1
	2 decreased function alleles	1
Intermediate metabolizer	1 no function + 1 decreased function alleles	0.5
Poor metabolizer	2 no function alleles	0

Pharmacogenetics of drug metabolism can increase accuracy of drug and dose selection

- Perform testing to predict metabolic phenotypes (per gene)
- Apply relevant clinical and gene-based dosing guidelines (per drug)
- Counsel and monitor
 - Avoid interactions
 - Evaluate response
 - Optimize dose



Sources of dosing guidance



Pharmacogenomics Knowledge Base (pharmgkb.org)

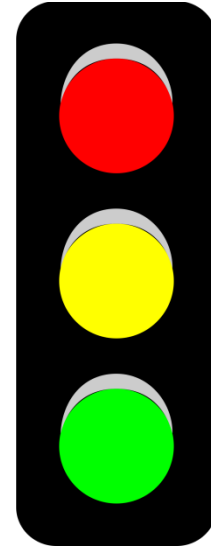
- Gene-based dosing guidelines
 - Clinical Pharmacogenetics Implementation Consortium (CPIC)
 - Dutch Pharmacogenomics Working Group (DPWG)
- Clinical annotations (>3000)

Other Sources:

- FDA labeling and “Table of Pharmacogenomic Biomarkers in Drug Labels” and “List of Cleared or Approved Companion Diagnostic Devices”
- International drug labeling (European Union, Japan, Canada, etc.)
- Professional Society Guidelines
- Software tools and algorithms (public and proprietary)

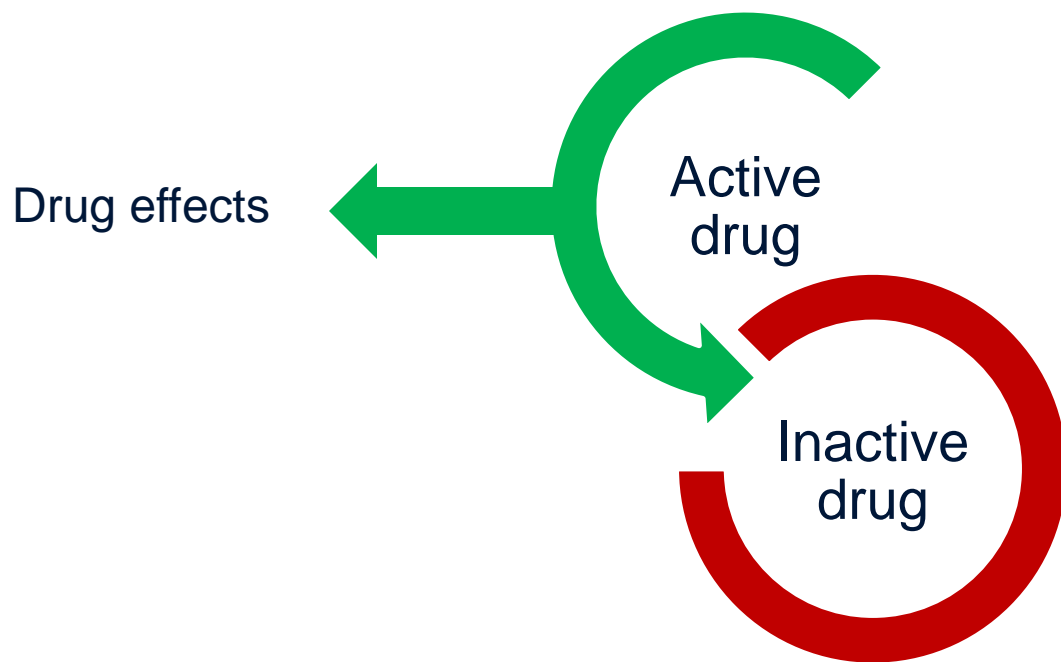
Examples of dosing guidance

- ***Drug avoidance*** due to risk of toxicity
- ***Drug avoidance*** due to predicted lack of efficacy
- Dose adjustment and optimization

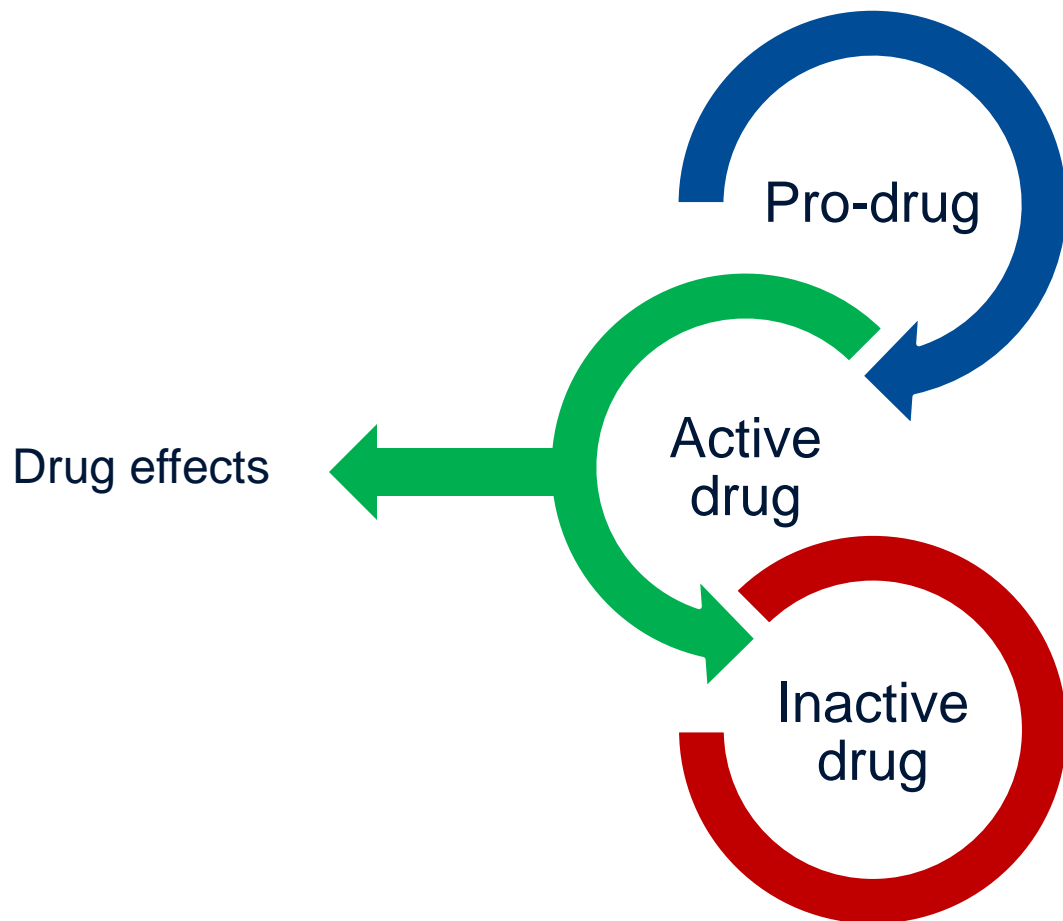


Must know what the consequence of metabolism is for an individual drug...

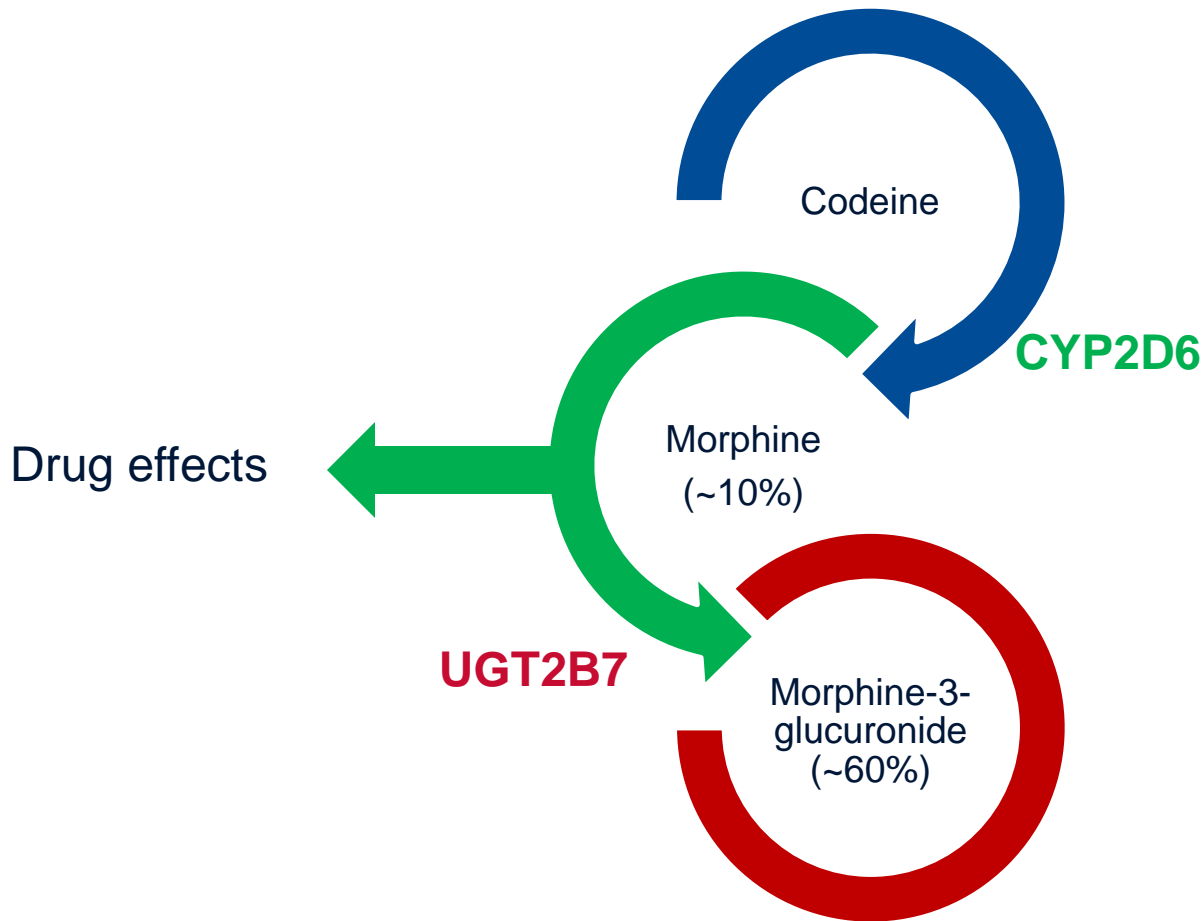
Drug analytes may be “active” or “inactive”



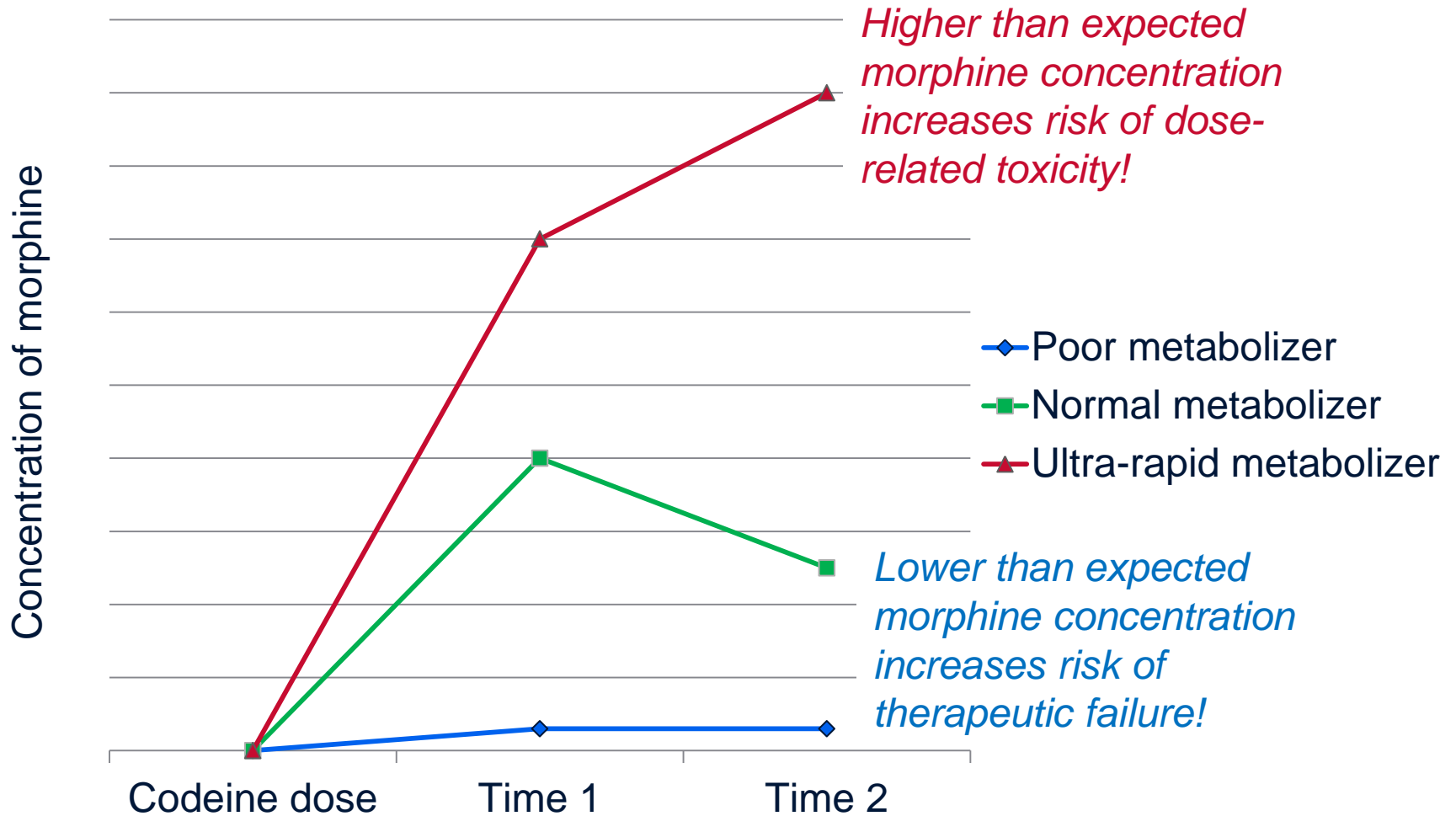
Drug analytes may be “active” or “inactive”



Simplified metabolism of codeine



CYP2D6 phenotypes are associated with the amount of morphine generated from codeine



CPIC guidance for extreme CYP2D6 phenotypes

- **Ultra-rapid metabolizers:** avoid codeine use due to potential for toxicity
- **Poor metabolizers:** avoid codeine use due to lack of efficacy

“Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity... To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone, along with non-opioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultra-rapid metabolizers.”

<https://www.pharmgkb.org/guideline/PA166104996>

Examples of other CYP-based dosing guidelines

- CYP2D6
 - Tricyclic antidepressants
 - SSRI antidepressants
 - Antipsychotics
 - Opioids
 - Tamoxifen
 - Propafenone
- CYP2C9
 - Phenytoin
 - Warfarin
 - Antihyperglycemics
- CYP2C19
 - Tricyclic antidepressants
 - SSRI antidepressants
 - Clopidogrel
 - Voriconazole
- CYP3A4/CYP3A5
 - Tacrolimus

<https://www.pharmgkb.org/>
<https://cpicpgx.org>

Pharmacogenomics Research Network

Translational Pharmacogenetics Program

- University of Maryland
- University of Florida
- St Jude Children's Research Hospital
- Vanderbilt University
- Mayo Clinic
- Ohio State University

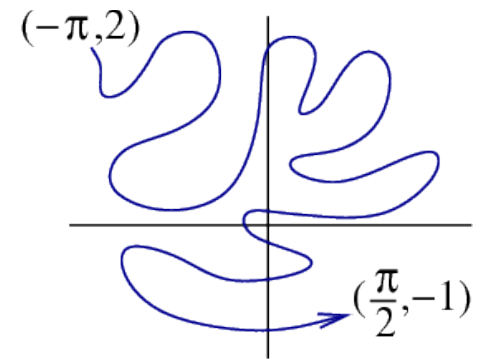


*Active
implementation
sites*

Shuldiner et al., *Clin Pharmacol Ther*, 94(2):207-10, 2013

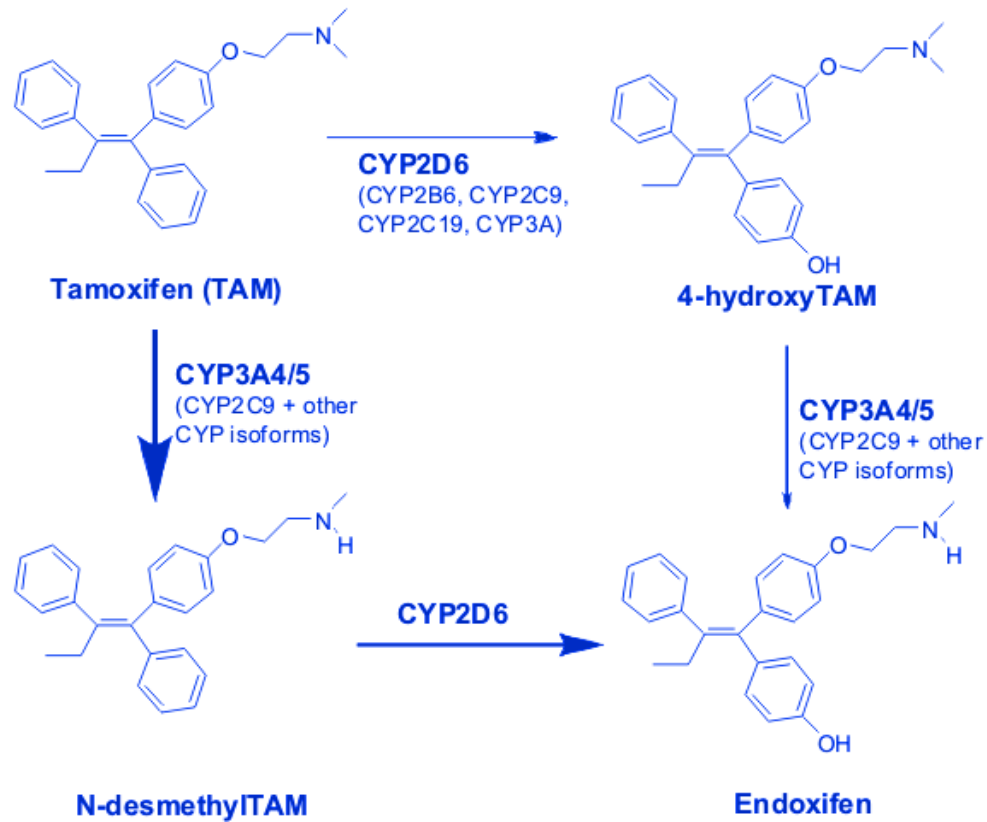
Metabolism isn't always simple

- Most drugs are metabolized by many enzymes
- The balance of metabolic activity will influence the optimal dose of a drug
- Drug-drug and food-drug interactions can change the phenotype of one or multiple pathways
- Therapeutic concentrations of a drug does not guarantee response



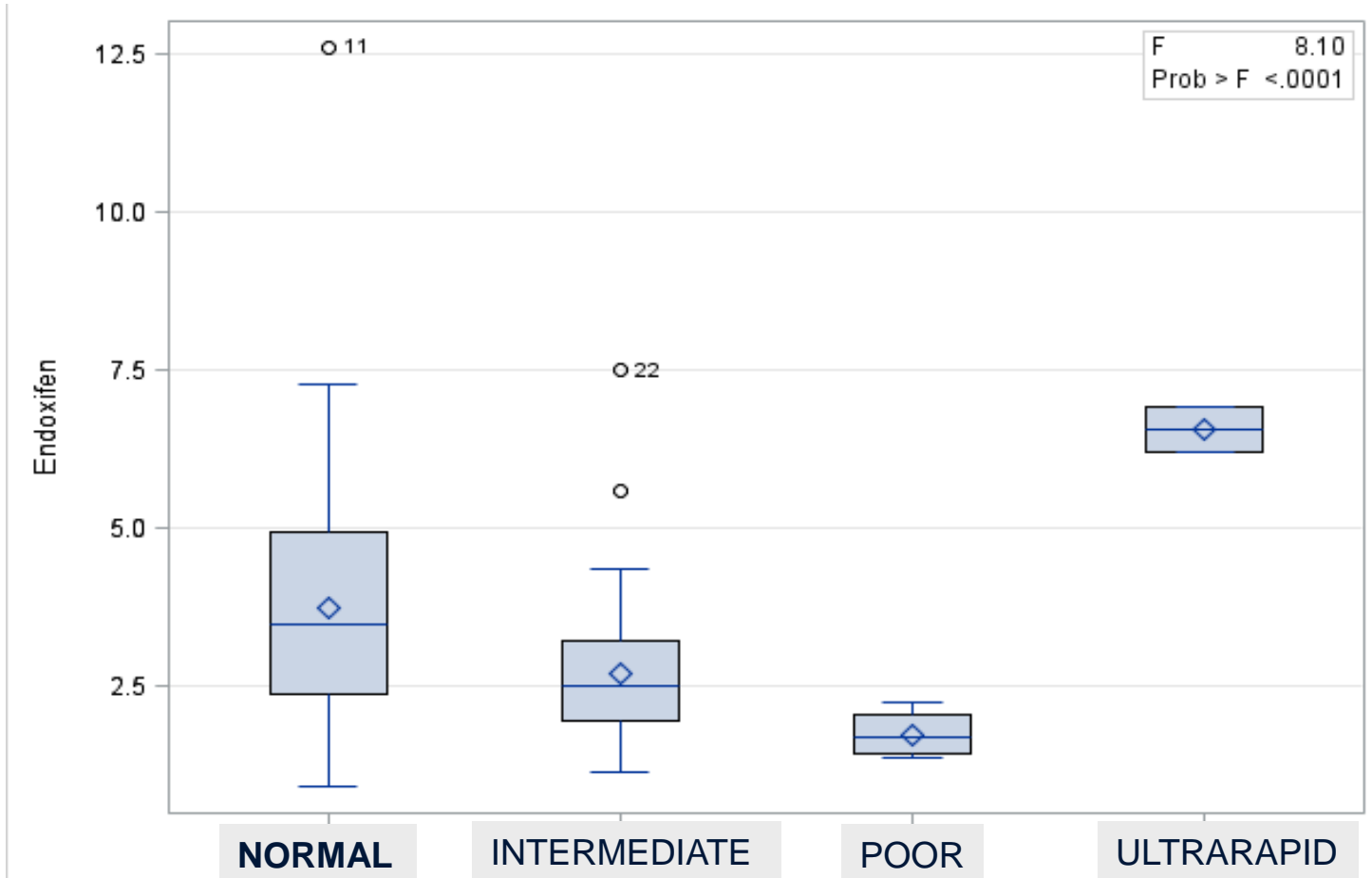
Simplified metabolism of tamoxifen

- Involves multiple drug metabolizing enzymes
- Complicated interactions of genetic and non-genetic factors
- Therapeutic range not well established



Powers et al, *J Clin Pharmacol*, 2016

Association of CYP2D6 phenotype and endoxifen concentrations



Powers et al, *J Clin Pharmacol*, 2016

Multi-gene software/algorithmic approach

- Proprietary commercial products are available
 - GeneDose™ – many drug classes
 - YouScript® – many drug classes
 - GeneSight® – psychotropics, ADHD, analgesics
 - CNSDose – antidepressants
- Some integrate genetics with clinical and demographic data and/or offer interactive risk mitigation tools for polypharmacy
- All tools provide decision support tools but few are supported by randomized clinical trials, and no studies directly compare effectiveness of the clinical decision support



Bousman C, *Lancet Psychiatry*, 2016

Multi-gene software case example

Medication Summary (more alternatives discoverable at GeneDose™ LIVE)

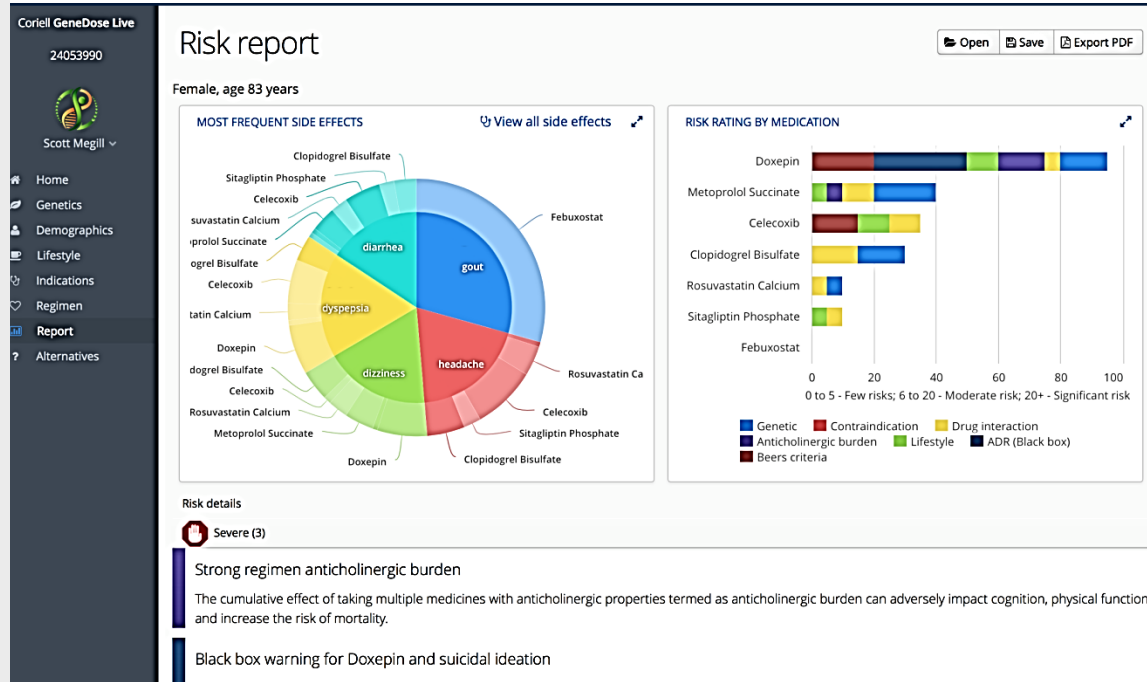
Therapeutic Class  Standard Precautions   Caution / Info  Consider Alternatives

Anti-ADHD Agents		Atomoxetine	
Antiarrhythmics		Flecainide Propafenone	
Anticoagulants		Acenocoumarol	
Anticonvulsants		Phenytoin	
Antidementia Agents		Donepezil	
Antidepressants	Flupenthixol Mirtazapine	Amitriptyline Clomipramine Desipramine Doxepin Duloxetine Nortriptyline Protriptyline Venlafaxine Vortioxetine	
Antidiabetics	Glibenclamide Gliclazide Glimepiride Tolbutamide		
Antifungals			
Antiplatelet Agents		Clopidogrel	
Antipsychotics	Olanzapine	Aripiprazole Clozapine Haloperidol Risperidone Zuclopenthixol	Thioridazine

Gene	Genotype	Phenotype
<i>CYP2D6</i>	*4/*4	Poor
<i>CYP2C19</i>	*2/*1	Intermediate
<i>CYP2C9</i>	*17/*1	Rapid
<i>CYP3A5</i>	*3/*1	Intermediate

GeneDose LIVE

- Cloud-based software tool
- Incorporates both genetic and nongenetic risk factors, lifestyle factors, drug-drug interactions, Beers criteria, etc.
- Includes >35,000 drug products
- Mitigates risk of adverse drug reactions



Real time modeling of alternative drug choices

ell GeneDose Live

Alternatives for Doxepin Hydrochloride 150mg Oral capsule

Tricyclic and other cyclic Antidepressants

Alternative drug	Δ drug	Δ regimen ▲	Detail	Risk chart	Est. cost/dose
<input type="checkbox"/> Maprotiline Hydrochloride Oral tablet	-80	-90	⊕		Generic: \$1.18
<input type="checkbox"/> Mirtazapine Oral disintegrating tablet	-50	-60	⊕		Brand: \$4.06 Generic: \$0.94
<input type="checkbox"/> Mirtazapine Oral tablet	-50	-60	⊕		Brand: \$4.89 Generic: \$0.44
<input type="checkbox"/> Amitriptyline Hydrochloride Oral tablet	-40	-50	⊕		Generic: \$0.65
<input type="checkbox"/> Amoxapine Oral tablet	-35	-45	⊕		Generic: \$1.02
<input type="checkbox"/> Protriptyline Hydrochloride Oral tablet	-25	-35	⊕		Brand: \$4.09 Generic: \$1.64
<input type="checkbox"/> Trimipramine Maleate Oral capsule	-20	-30	⊕		Brand: \$5.73 Generic: \$3.05
<input type="checkbox"/> Imipramine Hydrochloride Oral tablet	-18	-28	⊕		Brand: \$7.93 Generic: \$0.13
<input type="checkbox"/> Doxepin Hydrochloride Oral capsule	-	-	⊕		Brand: \$19.02

[Update alternatives model](#)

Risk scores represent the cumulative total of warnings from sources such as the Food and Drug Administration, the American Geriatric Society, pharmaceutical labeling, medical publications, and research in genetics. Each risk has been weighted according to the impact severity associated with that risk. These results are intended to complement the complete medical records for this patient and should be used only by a qualified healthcare provider.

Models for implementation of multi-gene pharmacogenetic testing

- Application-based (e.g. psychiatry)
 - Pre-emptive
 - Reactive
- Not specific to an application
 - Elderly patients on polypharmacy
 - Personal or family history of adverse drug reactions
 - Wellness panels



Examples of positive outcomes from multigene pharmacogenetic testing

- Improved antidepressant efficacy
 - 2.52-fold greater rate of remission of major depressive disorder with testing (Singh, *Clin Psychopharmacology Neuroscience*, 2015)
- Reduced pharmacy costs
 - \$1035.60 savings over 1 yr in total medication costs with testing in cohort of psychiatric patients (Winner et al, *Current Medical Research & Opinion*, 2015)
- Reduced rates of hospitalization
 - 9.8% with testing versus 16.1% without testing in cohort of patients ≥ 65 yrs (Brixner et al, *J Medical Economics*, 2015)
- Improved adherence with therapy

Are more genes better?

- In a review of 22 proprietary algorithms for clinical validity, there were 46 genes represented (Bousman, *Lancet Psychiatry*, 2016)
 - 25 (53%) were associated with supporting evidence graded by the PharmGKB databased as preliminary or low
 - 9 (20%) were associated with high levels of evidence, only 3 of which are relevant to psychotropics: *CYP2D6*, *CYP2C19* and *HLA-B*
 - All algorithms include *CYP2D6* and *CYP2C19*; most also include *CYP2C9* and *CYP3A4/5*
- 39.1% of patients ≥ 65 receive at least one drug metabolized by *CYP2D6*, *CYP2C19* and/or *CYP2C9* (Kuch et al, *Health Informatics*, 2016)

Conclusions

- CYP pharmacogenetics can help guide drug and dose selection for an individual patient, particularly to minimize adverse drug reactions and therapeutic failure.
- Pharmacogenetic testing does not replace the need for dose optimization or clinical monitoring.
- Patients and providers should be recognized that the field of clinical pharmacogenetics is evolving and guidelines continue to improve.



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