Pharmacogenomics for the Pharmacist

Women in Pharmacy

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Why Pharmacogenomics?

"The Right Med at the Right Dose for the Right Patient"

- Reduce Toxicity (Pharmacokinetics→Supratherapeutic; Predict Drug Allergy)
- Improve Efficacy (Pharmacokinetics→Subtherapeutic; Pharmacodynamics→Receptor Affinity

Leading causes of Death in US 2013

- **Heart disease: 611,105**
- **Cancer: 584,881**
- ***Medical Errors 251,454 (2013)** –Not included in CDC list*
- Chronic lower respiratory diseases: 149,205
- Accidents (unintentional injuries): 130,557
- Stroke (cerebrovascular diseases): 128,978
- ***Adverse Drug Reactions 106, 000 (1994)** –Not included in CDC list*
- Alzheimer's disease: 84,767
- Diabetes: 75,578
- Influenza and Pneumonia: 56,979
- Nephritis, nephrotic syndrome, and nephrosis: 47,112

Source: Deaths: final data. CDC
Makary et al BMJ 2016;353:i2139
Lazarou et al, JAMA, 279: 1200-5, 1998

Why Pharmacists?

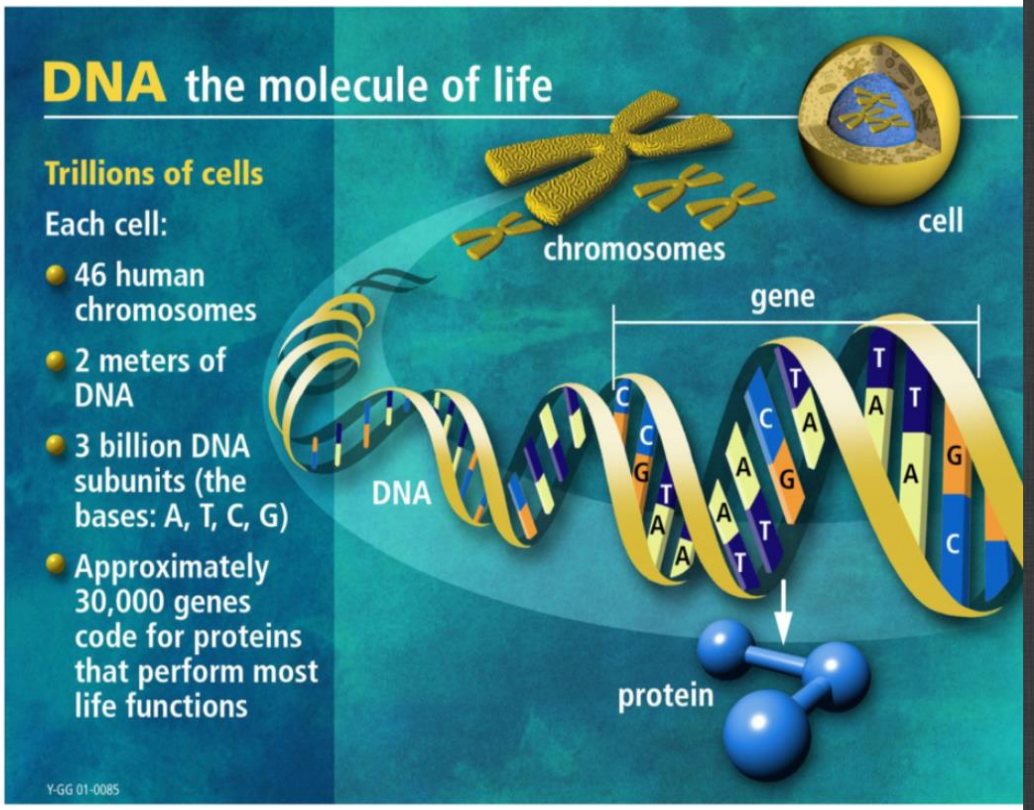
- In Oncology, Physician/Pharmacist teams are applying these concepts to Precision Medicine, but not to Outpatient Medicine
- For Outpatient Medicine, pharmacists are leading this movement, as they are uniquely positioned to have the knowledge base to interpret PGx testing and apply those results to a patient's current regimen

DNA Transcription & Translation

Nomenclature in Genetics

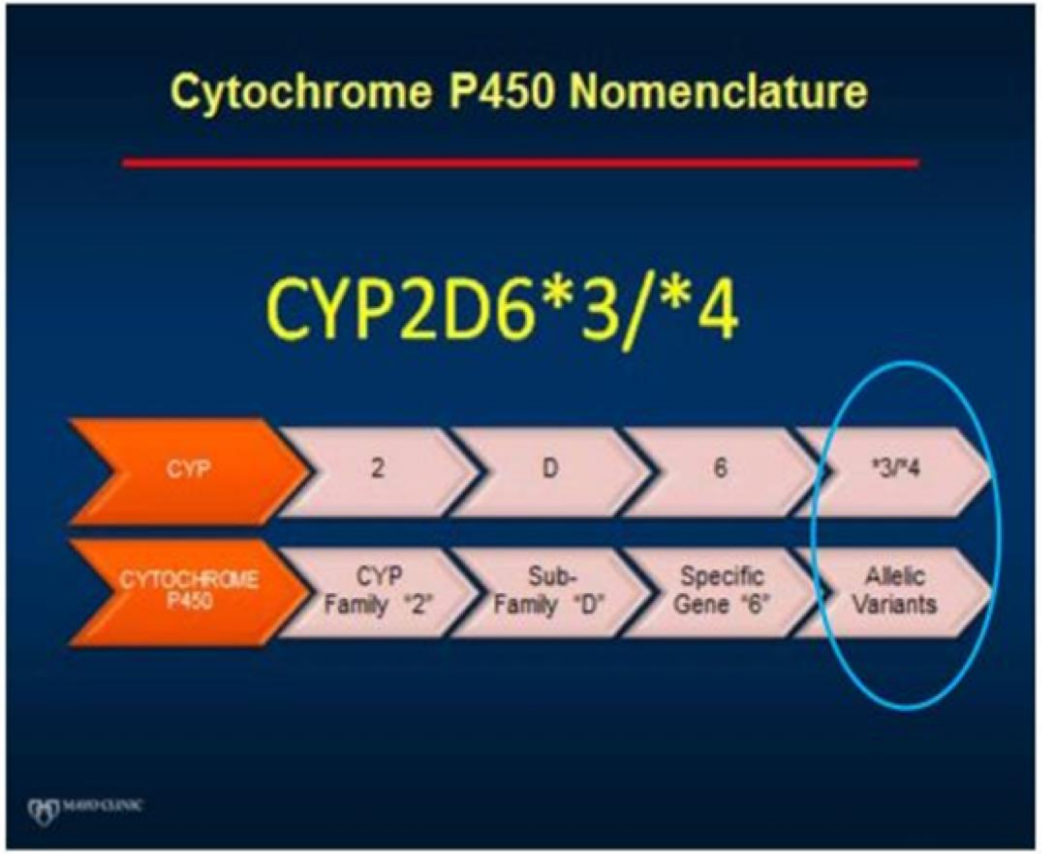
Key Genomic Concepts

- Chromosome: 23 pairs of tightly coiled DNA
- Genes:
  - Alleles are forms of the same gene with small differences in the DNA sequence (genetic variants)
- DNA: Hereditary material composed of 4 chemical bases (A, T, C, G)



http://www.ncbi.nlm.nih.gov

Genetics Home Reference http://ghr.nlm.nih.gov



Genotype: result of a pair of alleles

CYP2D6*3/*4 is a genotype.

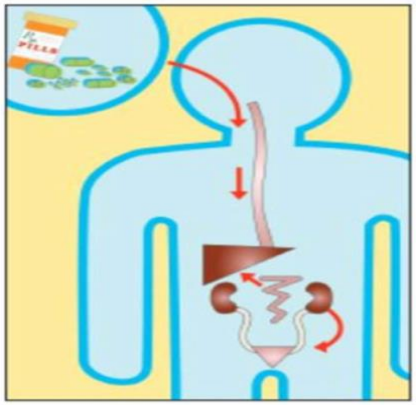
This is a genetic lab result.

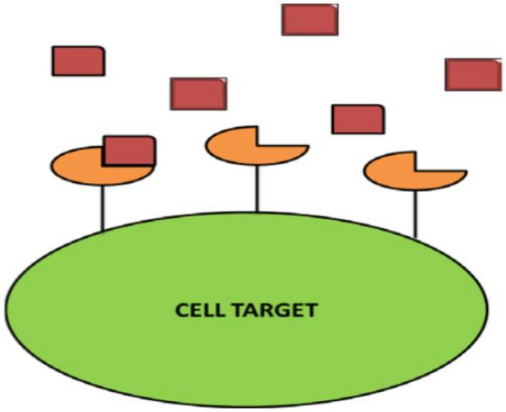
Pharmacogenomics (PGx) – The Basics

Human Genome Project

- >$3 billion, to map 3 billion base pairs
- PGx looks for Single Nucleotide Polymorphisms (SNPs)
- These “Mutations” are now called “Variants”
- “*1/*1” is the internationally agree upon norm
- Other numbers based on time of discovery (“*1/*17”)
- SNPs can affect structure, which affect function:
- For an enzyme/transporter, can affect **Pharmacokinetics**
- For a receptor, **Pharmacodynamics**

PK, PD





Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination

Genetic Variants

Pharmacodynamics

- Pharmacologic effect
- Toxic effect
  - Receptors
  - Intracellular targets
  - Ion channels

PGx - continued

Pharmacokinetics (PK)

1. Enzymes:

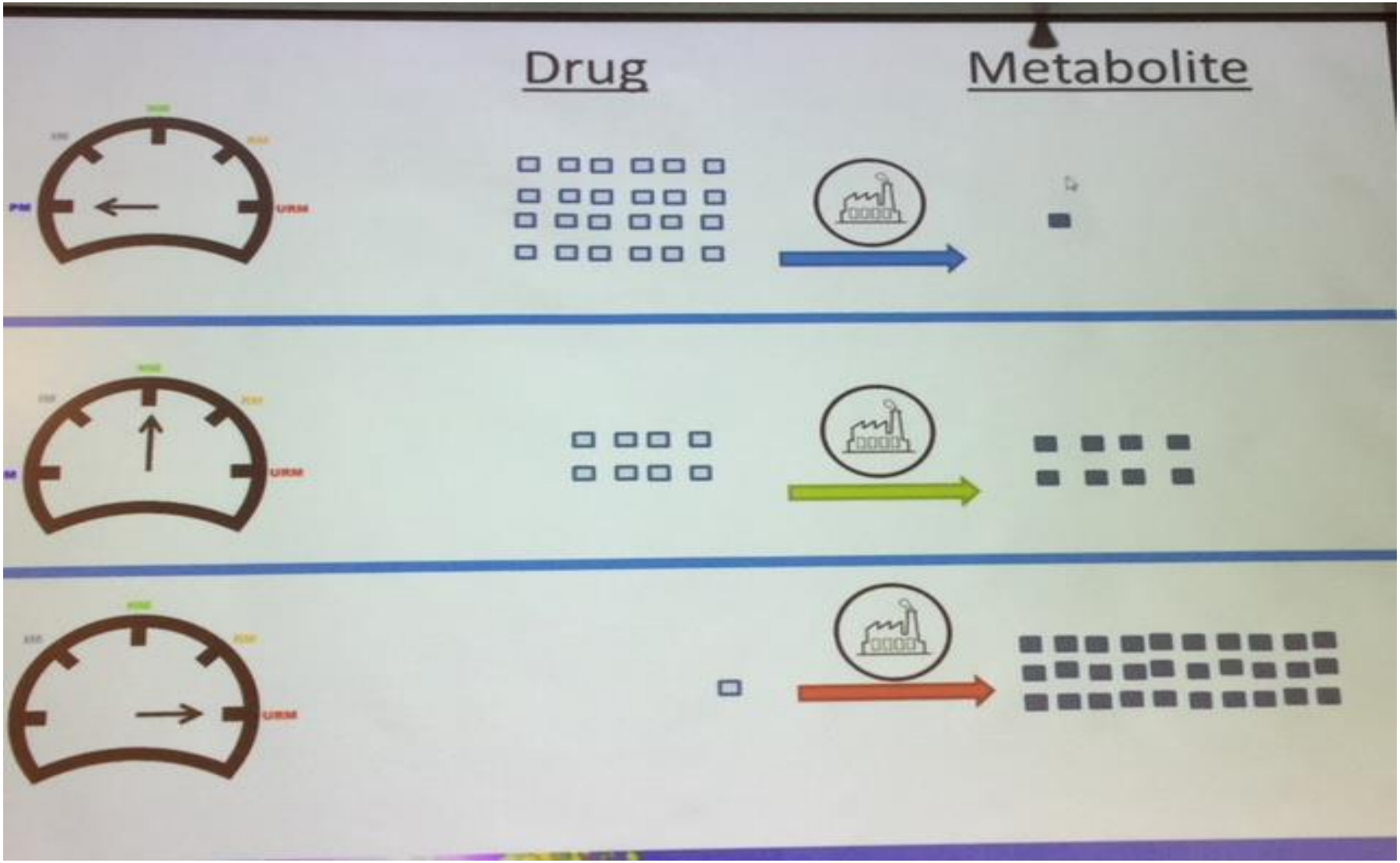
- Ultrarapid Metabolizer (UM)
- Rapid Metabolizer (RM)
- Extensive (Normal) Metabolizer (EM)
- Intermediate Metabolizer (IM)
- Poor Metabolizer (PM)

Drug→Metabolite; ProDrug→Active Drug

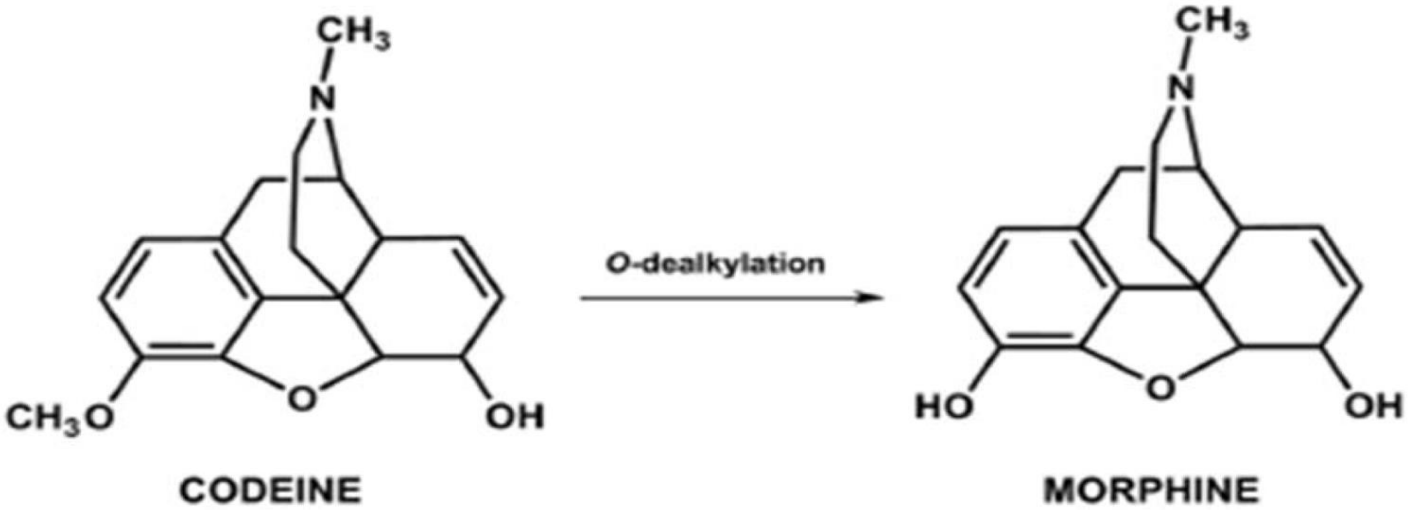
Gene-Drug-Drug Interactions (Inducers/Inhibitors)

2. Transporters

Pharmacokinetics (PK)- Drug Metabolism



PK – ProDrug Activation



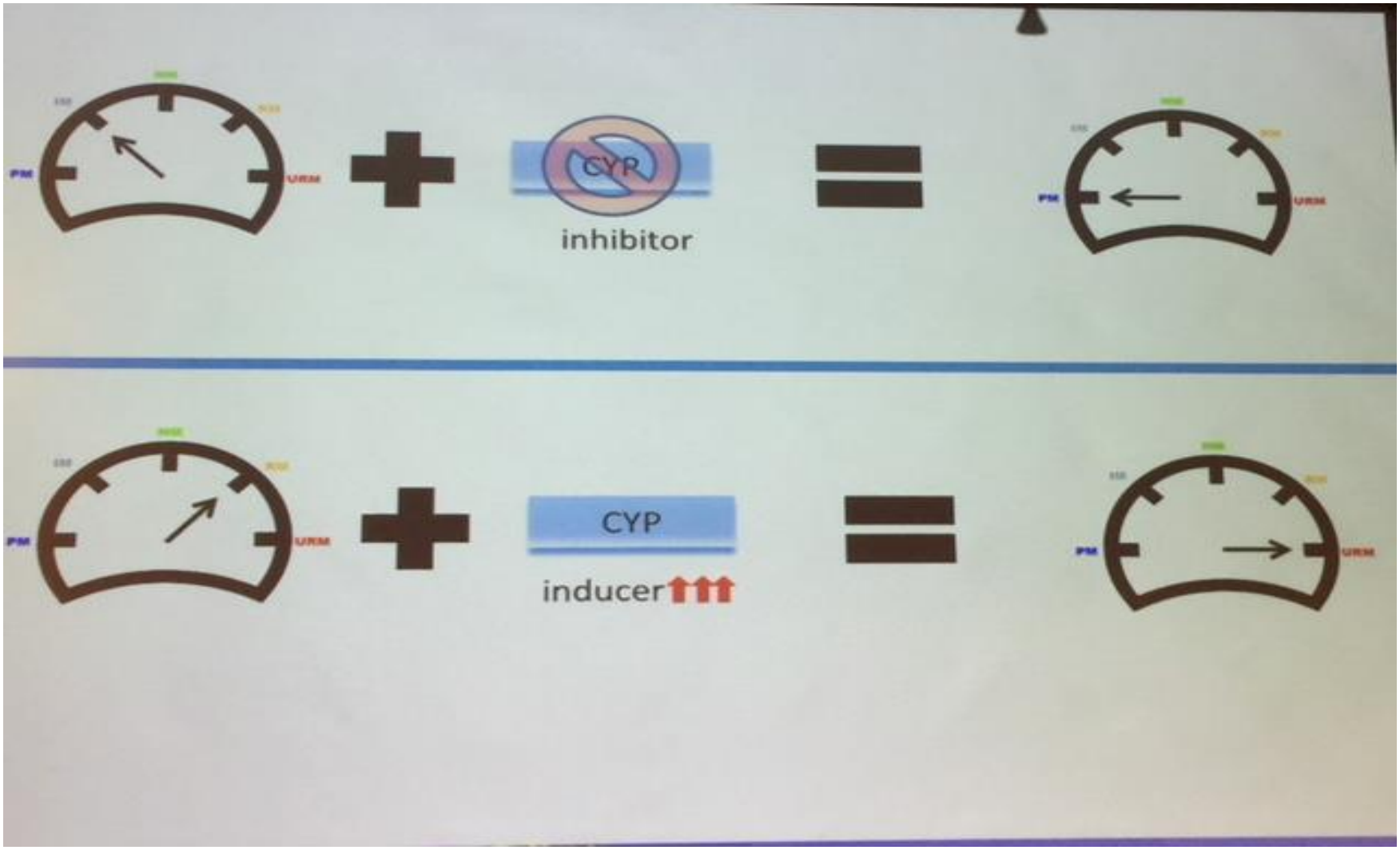
CODEINE MORPHINE

Prodrug	Metabolized form	Increase in binding potency
Codeine	Morphine	300 - 7000
Oxycodone	Oxymorphone	14 - 64
Hydrocodone	Hydromorphone	7 - 33

CYP2D6 Metabolizer Phenotypes	Active Drug	Pro-Drug
ULTRA-RAPID	Rapid metabolism	Activation
RAPID (NORMAL-ULTRA-RAPID)		
NORMAL (EXTENSIVE)		
INTERMEDIATE		
POOR	Drug accumulates	No activation

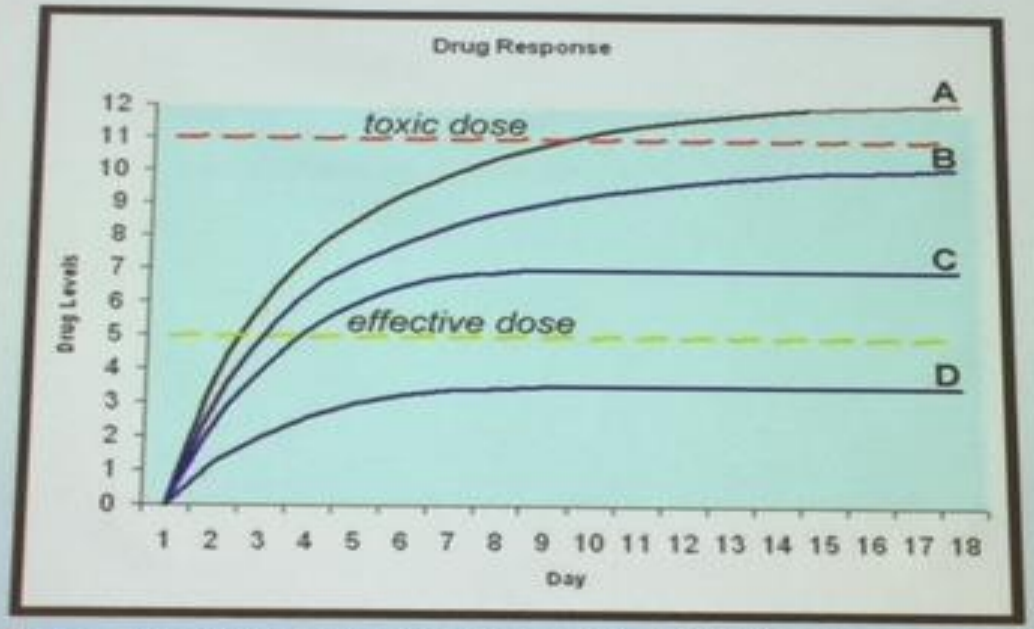
http://www.ncbi.nlm.nih.gov; Genetics Home Reference http://ghr.nlm.nih.gov

Gene-Drug Interactions



Pharmacokinetics

Pharmacogenetic Effect



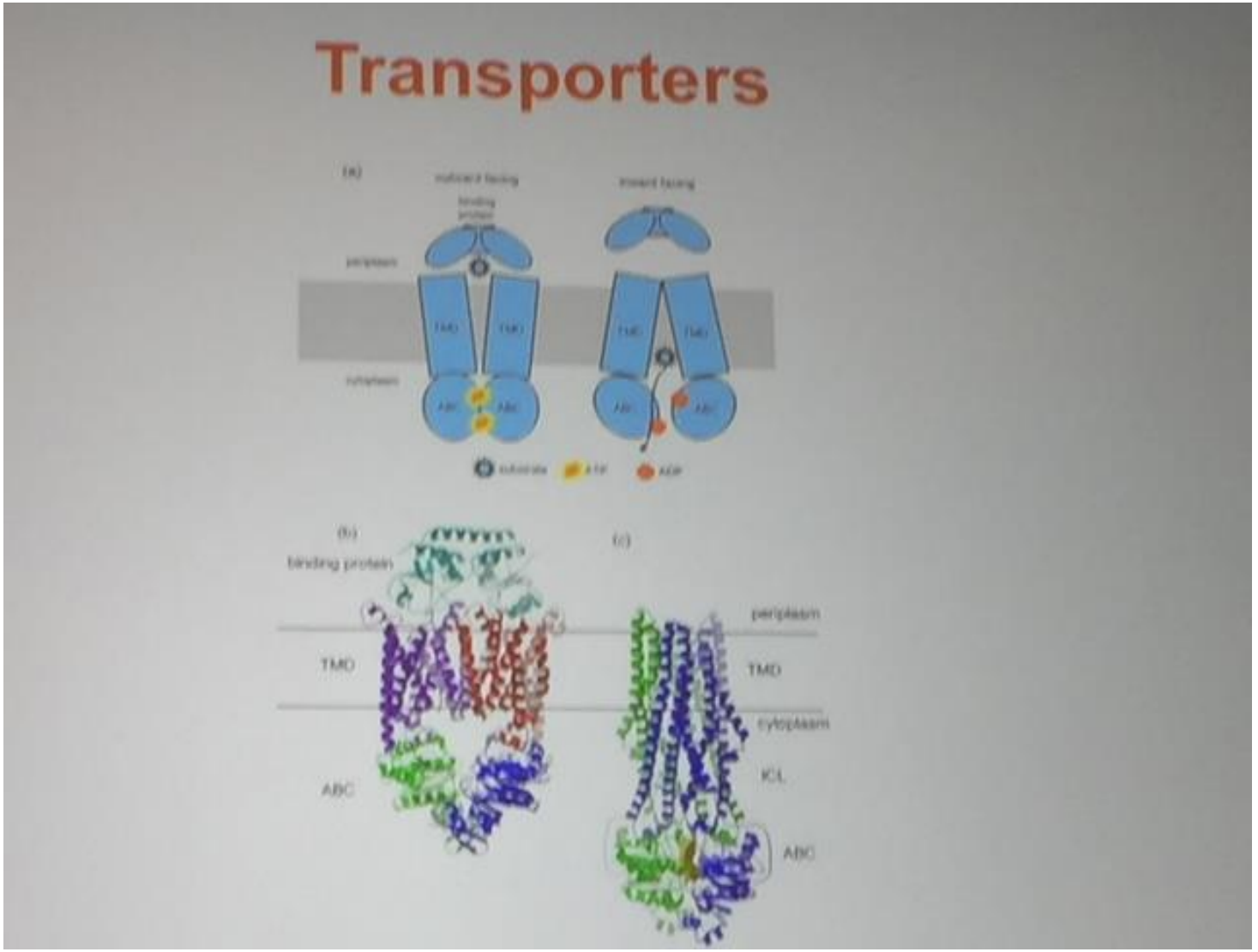
A. **PM** poor metabolizer, absent or greatly reduced ability to clear or activate drugs or move a pro-drug to active metabolite.

B. **IM** intermediate metabolizer. Heterozygotes for normal and reduced activity genes.

C **EM** extensive metabolizer *"normal metabolizers"*.

D. **UM** Ultra-rapid metabolizer Greatly increased activity accelerating clearance or activation

Transporters

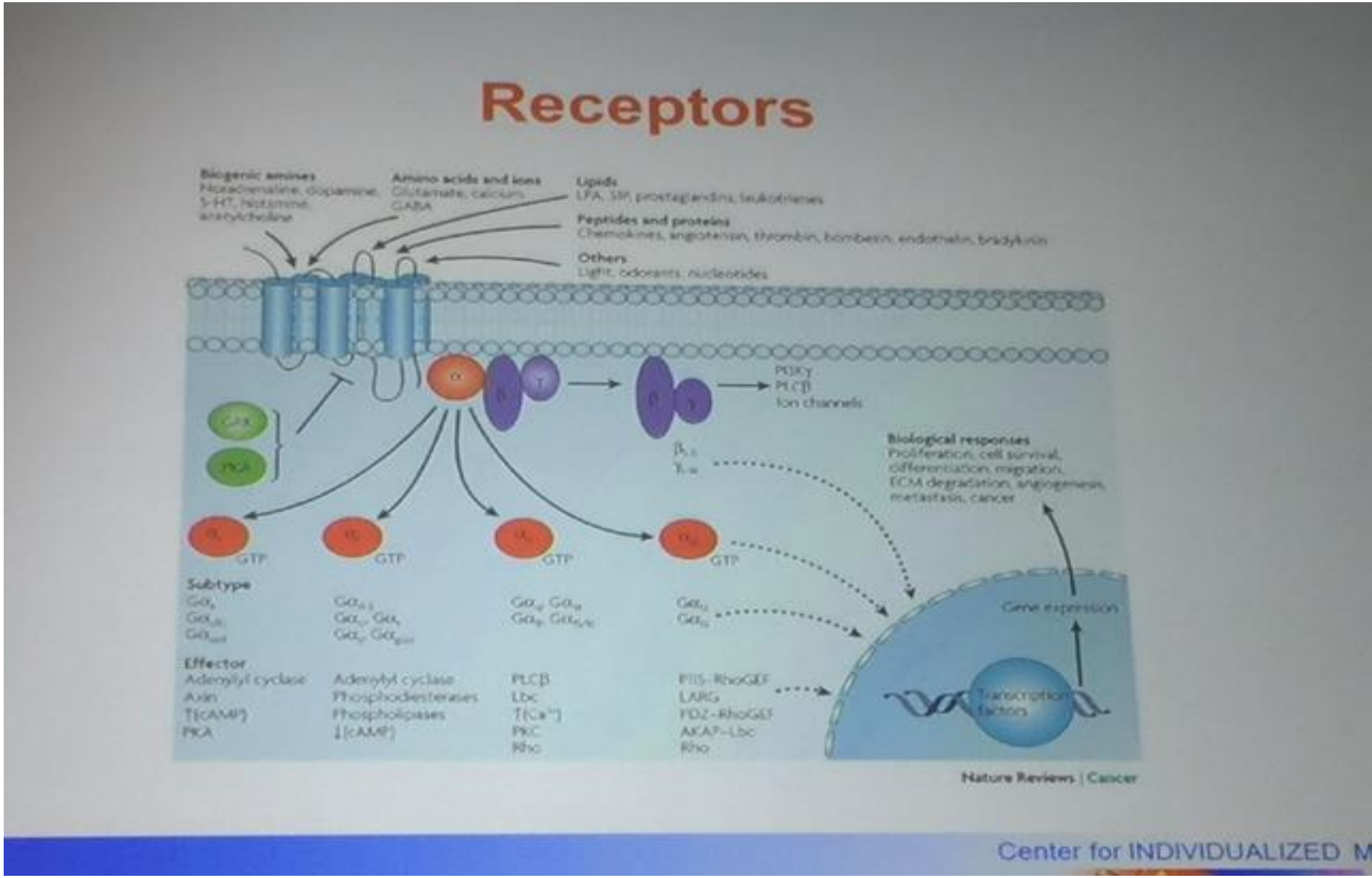


PGx-continued

Pharmacodynamics (PD)

- “Qualitative” assessment of Receptor Affinity
- Genes code for structure, and structure equals function, but downstream effects are more complicated than predicting metabolism in PK

Receptors

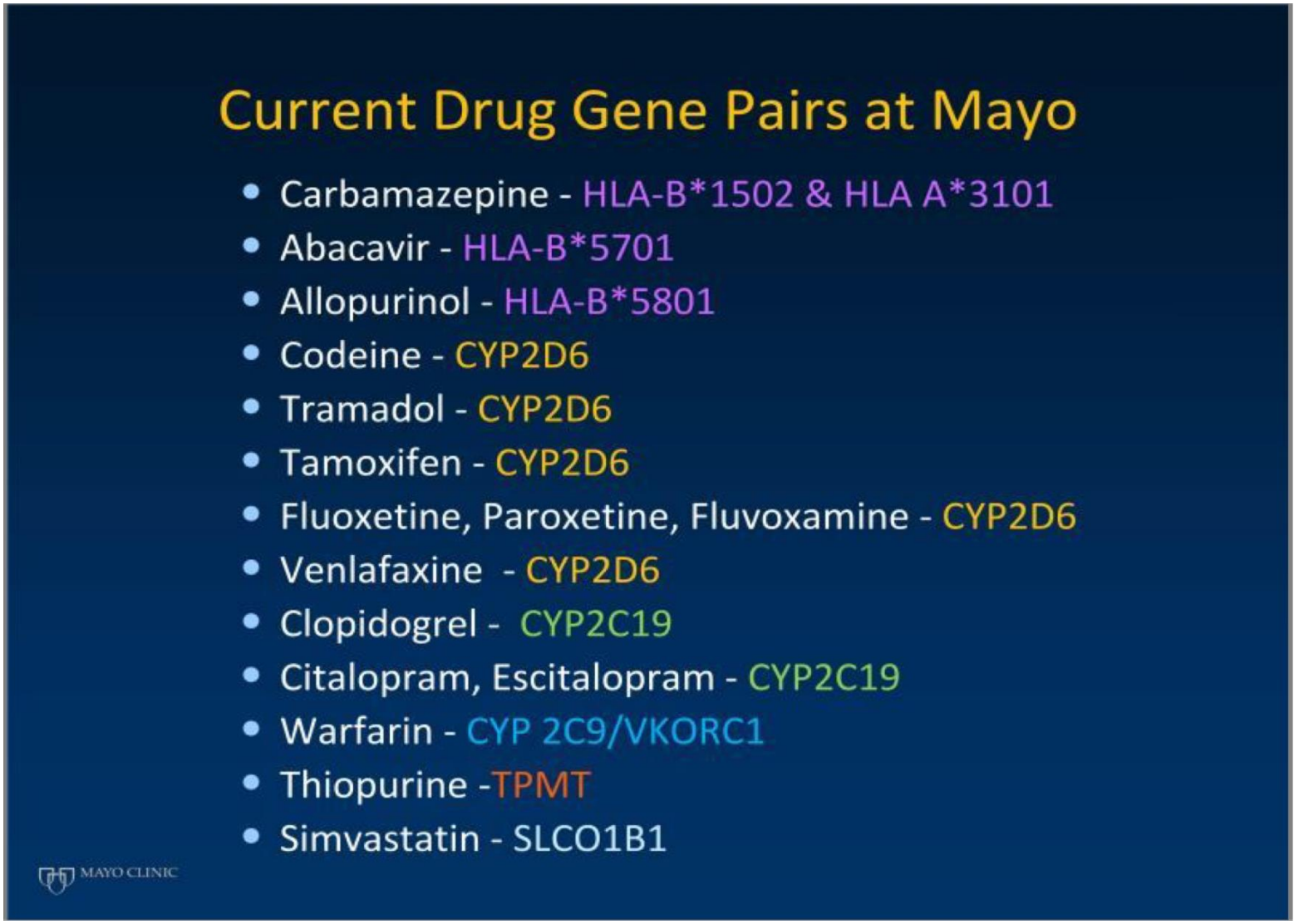

Receptors
Biogenic amines
Noradrenaline, dopamine, 5-HT, histamine, acetylcholine
Amino acids and ions
Glutamate, calcium, GABA
Lipids
LPA, S1P, prostaglandins, leukotrienes
Peptides and proteins
Chemokines, angiotensin, thrombin, bombesin, endothelin, bradykinin
Others
Light, odorants, nucleotides
PI3Kγ
PLCβ
Ion channels
Biological responses
Proliferation, cell survival, differentiation, migration, ECM degradation, angiogenesis, metastasis, cancer
GTP
GTP
GTP
GTP
Subtype
Effector
Adenylyl cyclase
Axin
↑[cAMP]
PKA
Adenylyl cyclase
Phosphodiesterases
Phospholipases
↓[cAMP]
PLCβ
Lbc
↑[Ca2+]
PKC
Rho
PDZ-RhoGEF
LARG
AKAP-Lbc
Rho
Gene expression
Transcription factors
Nature Reviews | Cancer

PGx - continued

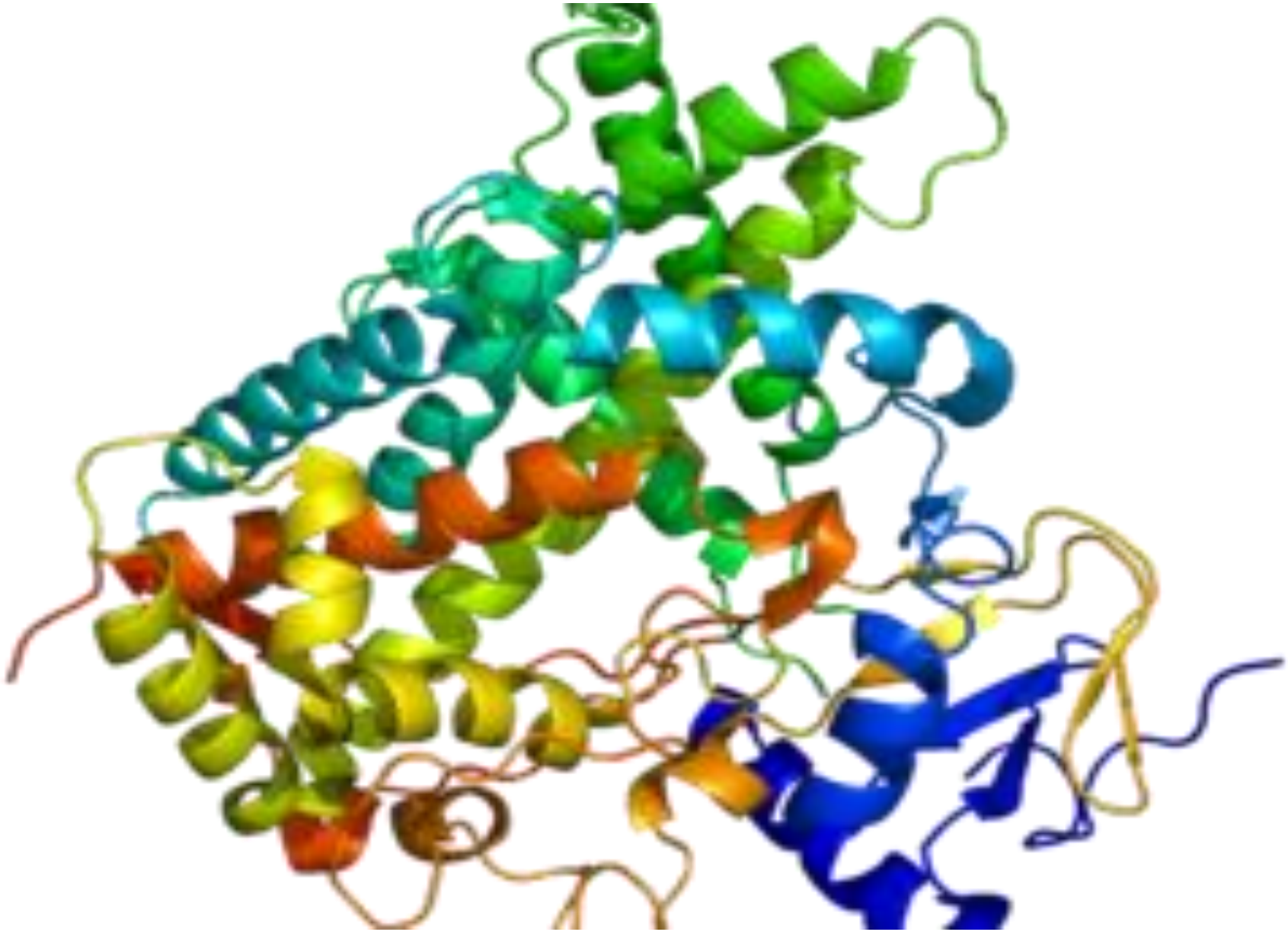
Predicting Severe Drug Allergy using HLA typing

- Carbamazepime: HLA-B*1502 & HLA-A*3101
- Abacavir: HLA-B*5701
- Allopurinol: HLA-B*5801

- HIGHLY PREDICTIVE OF SJS/TEN (ethnic variabilities to susceptibility (a/k/a “phenotypical expression”)

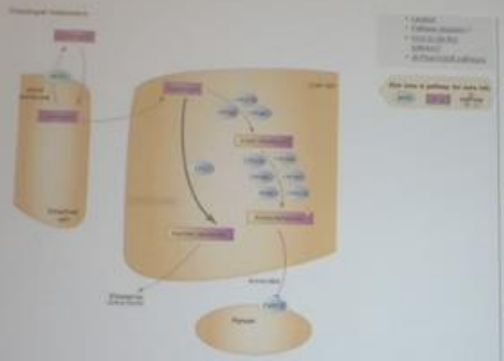


Top “Actionable” Drug-Gene Pairs at May Clinic



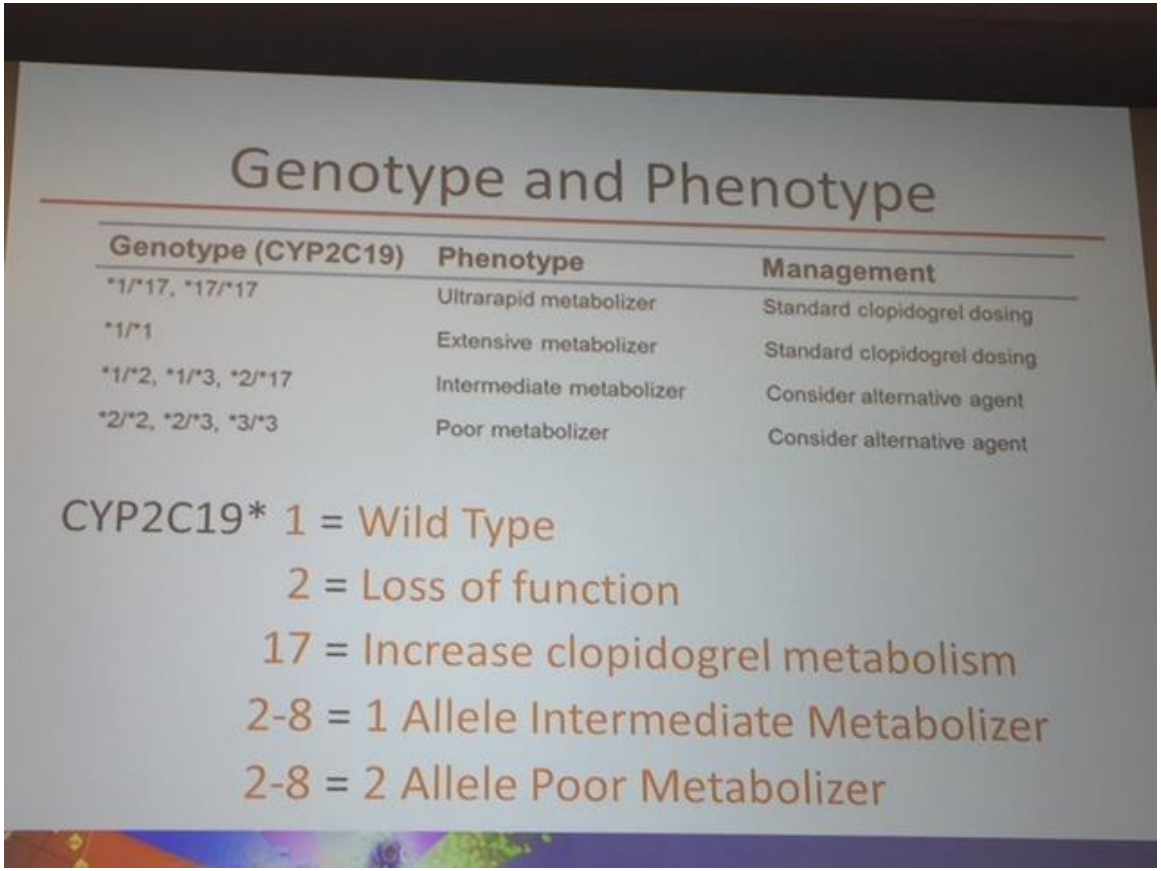
CYP2C19

Clopidogrel Mechanism of Action



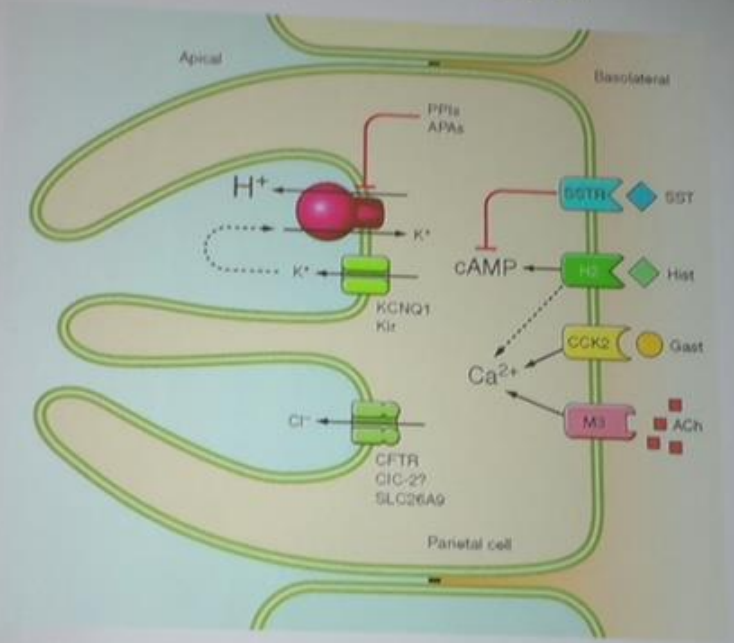
- Clopidogrel is a prodrug that requires CYP2C19 metabolism for activation
- The active metabolite of clopidogrel prevents platelet aggregation
- Poor CYP2C19 metabolism will reduce the efficacy of clopidogrel

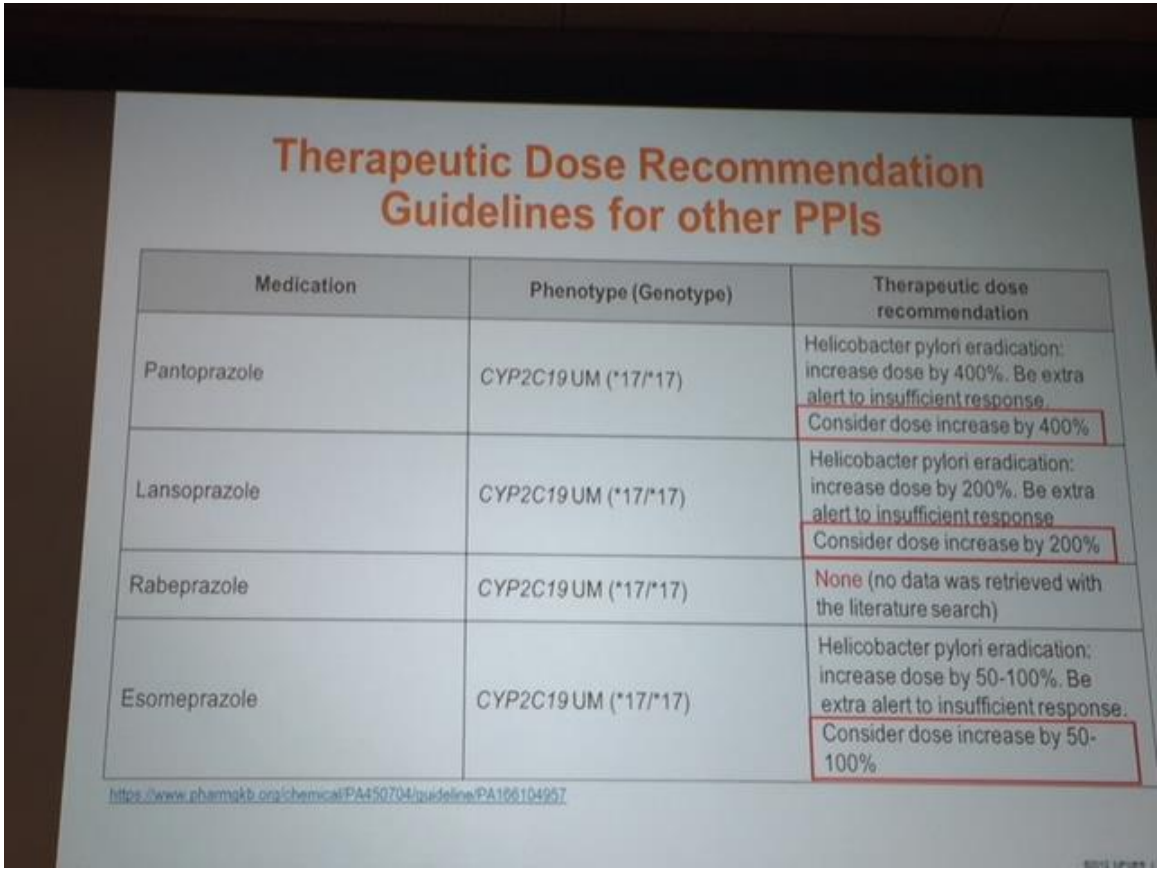
https://www.pharmgkb.org/pathway/PA154424674


Genotype and Phenotype
Genotype (CYP2C19)
Phenotype
Management
*1/*17, *17/*17
Ultrarapid metabolizer
Standard clopidogrel dosing
*1/*1
Extensive metabolizer
Standard clopidogrel dosing
*1/*2, *1/*3, *2/*17
Intermediate metabolizer
Consider alternative agent
*2/*2, *2/*3, *3/*3
Poor metabolizer
Consider alternative agent
CYP2C19* 1 = Wild Type
2 = Loss of function
17 = Increase clopidogrel metabolism
2-8 = 1 Allele Intermediate Metabolizer
2-8 = 2 Allele Poor Metabolizer

Proton Pump Inhibitors (PPI)

Mechanism of Action

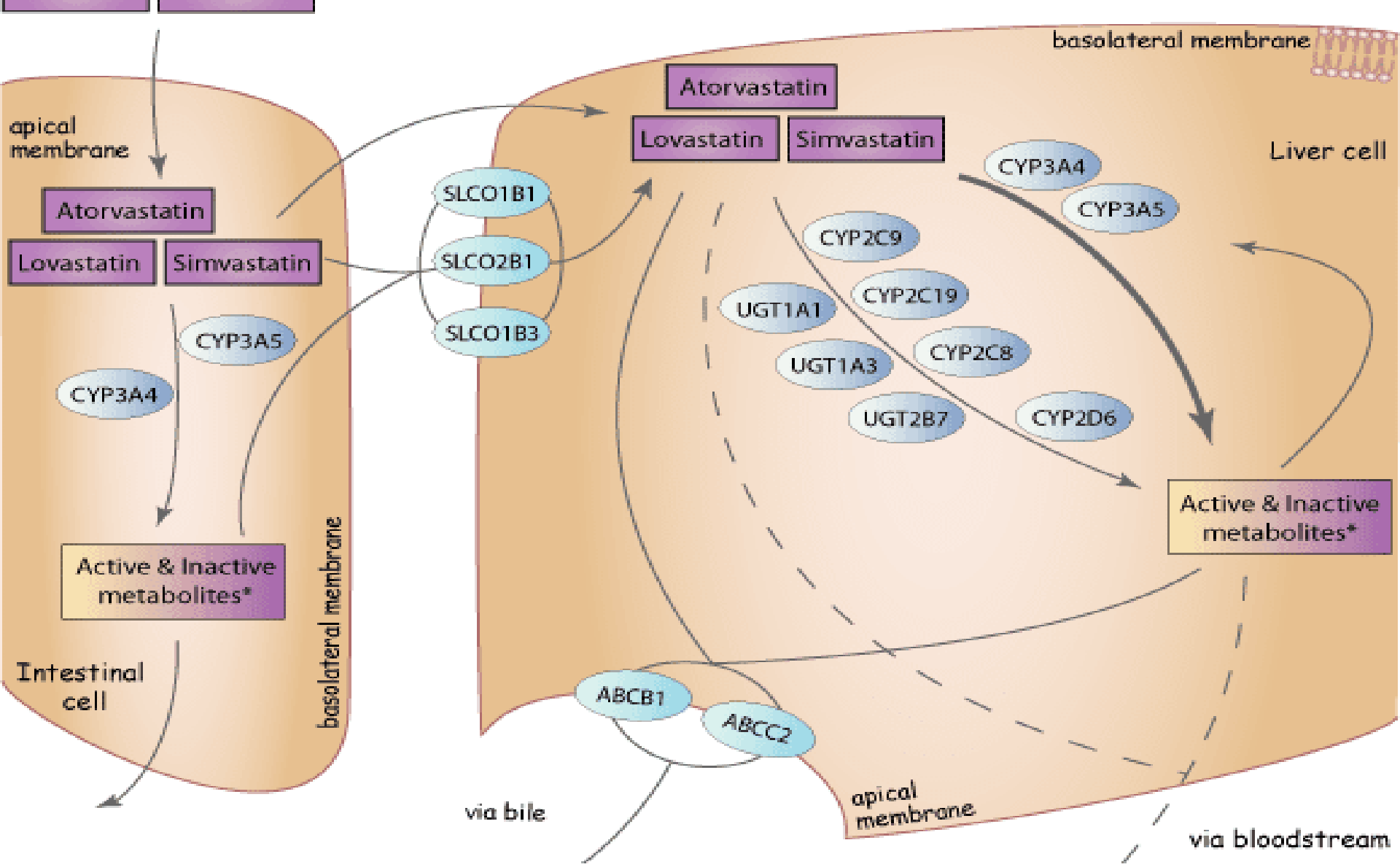




Therapeutic Dose Recommendation Guidelines for other PPIs

Medication	Phenotype (Genotype)	Therapeutic dose recommendation
Pantoprazole	*CYP2C19* UM (*17/*17)	Helicobacter pylori eradication: increase dose by 400%. Be extra alert to insufficient response. Consider dose increase by 400%
Lansoprazole	*CYP2C19* UM (*17/*17)	Helicobacter pylori eradication: increase dose by 200%. Be extra alert to insufficient response Consider dose increase by 200%
Rabeprazole	*CYP2C19* UM (*17/*17)	None (no data was retrieved with the literature search)
Esomeprazole	*CYP2C19* UM (*17/*17)	Helicobacter pylori eradication: increase dose by 50-100%. Be extra alert to insufficient response. Consider dose increase by 50-100%

https://www.pharmgkb.org/chemical/PA450704/guideline/PA166104957



SLCO1B1 Transporter

Putting It All Together

Relevant medications: 2C19, 1A2, 3A4

Enzyme	Substrate	Inhibitor	Inducer
CYP2C19	amitriptyline clomipramine desipramine (es)citalopram diazepam phenytoin omeprazole progesterone indomethacin propranolol	fluoxetine modafinil oxcarbazepine topiramate omeprazole ketoconazole	carbamazepine prednisone rifampin
CYP1A2	clozapine olanzapine haloperidol ondansetron caffeine	fluvoxamine ciprofloxacin cimetidine	insulin modafinil omeprazole **tobacco** char-grilled
CYP3A4, 5, 7	erythromycin (not 3A5) quinidine (not 3A5) alprazolam, diazepam, midazolam, zolpidem tacrolimus, cyclosporin buspirone, trazodone carbamazepine quetiapine, ziprasidone, lurasidone	Suboxone Indinavir… Ketoconazole fluconazole	carbamazepine **St. John's Wort** modafinil phenytoin

MAYO CLINIC

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P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
clozapine cyclobenzaprine duloxetine fluvoxamine haloperidol imipramine mexiletine nabumetone naproxen olanzapine riluzole tacrine2 theophylline tizanidine triamterene zileuton zolmitriptan	artemisinin bupropion[1] cyclophosphamide efavirenz[1] ifosfamide ketamine meperidine methadone nevirapine propofol selegiline	paclitaxel torsemide amodiaquine[2] cerivastatin repaglinide	**NSAIDs**: diclofenac ibuprofen naproxen piroxicam **Oral Hypoglycemics:** tolbutamide glipizide glyburide **Angiotensin II Blockers:** losartan irbesartan **Others:** celecoxib fluvastatin phenytoin rosiglitazone torsemide valproic acid warfarin zafirlukast	**PPIs**: esomeprazole lansoprazole omeprazole pantoprazole **Anti-epileptics:** diazepam phenytoin phenobarbitone **Others**: amitriptyline carisoprodol citalopram clomipramine clopidogrel cyclophosphamide imipramine labetalol proguanil voriconazole	**Beta Blockers:** carvedilol S-metoprolol propafenone timolol **Antidepressants:** amitriptyline clomipramine desipramine duloxetine fluoxetine imipramine paroxetine **Antipsychotics:** haloperidol risperidone thioridazine	**Anesthetics:** enflurane halothane isoflurane methoxyflurane sevoflurane **Others:** acetaminophen → NAPQI aniline benzene chlorzoxazone ethanol N,N-dimethyl formamide theophylline → 8-OH	**Macrolide antibiotics:** clarithromycin erythromycin (not 3A5) NOT azithromycin telithromycin **Anti-arrhythmics:** quinidine → 3-OH (not 3A5) **Benzodiazepines:** alprazolam diazepam → 3OH midazolam triazolam **Immune Modulators:** cyclosporine tacrolimus (FK506) sirolimus

Indiana University

P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
					Others: aripiprazole atomoxetine codeine dextromethorphan doxepine flecainide mexiletine ondansetron oxycodone risperidone tamoxifen		**HIV Antivirals:** indinavir ritonavir saquinavir nevirapine **Prokinetics**: cisapride **Antihistamines:** astemizole chlorpheniramine

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P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table

INHIBITORS

■ A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
■ A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
■ A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amiodarone ■ cimetidine efavirenz fluoroquinolones fluvoxamine[1] ticlopidine	clopidogrel thiotepa ticlopidine[2] voriconazole	■ gemfibrozil montelukast[1]	■ amiodarone efavirenz ■ fluconazole[2] isoniazid metronidazole paroxetine sulfamethoxazole voriconazole	cimetidine esomeprazole felbamate fluoxetine fluvoxamine isoniazid ketoconazole lansoprazole omeprazole oral contraceptives pantoprazole ticlopidine[2] voriconazole	■ bupropion ■ fluoxetine ■ paroxetine ■ quinidine[1] ■ duloxetine ■ amiodarone ■ cimetidine aripiprazole diphenhydramine chlorpheniramine clomipramine doxepin haloperidol methadone ritonavir terbinafine	disulfiram	**HIV Antivirals:** ■ indinavir ■ nelfinavir ■ ritonavir ■ clarithromycin ■ itraconazole ■ ketoconazole ■ nefazodone ■ erythromycin ■ grapefruit juice ■ verapamil[2] ■ suboxone ■ diltiazem ■ cimetidine amiodarone NOT azithromycin fluvoxamine troleandomycin voriconazole

Inhibitors

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P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table

INDUCERS

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
carbamazepine chargrilled meat rifampin tobacco	artemisinin carbamazepine efavirenz nevirapine phenobarbital phenytoin rifampin		carbamazepine nevirapine phenobarbital rifampin St. John's Wort	efavirenz rifampin ritonavir St. John's Wort		ethanol isoniazid	carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone

Inducers