Pharmacogenetics

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Objectives

- Understand the *allele nomenclature
- Differentiate between various metabolizers
- Recognize common drugs that can have adverse drug reactions

Pharmacogenetics

Precision Medicine by……

Getting the right dose to the right patient at the right time

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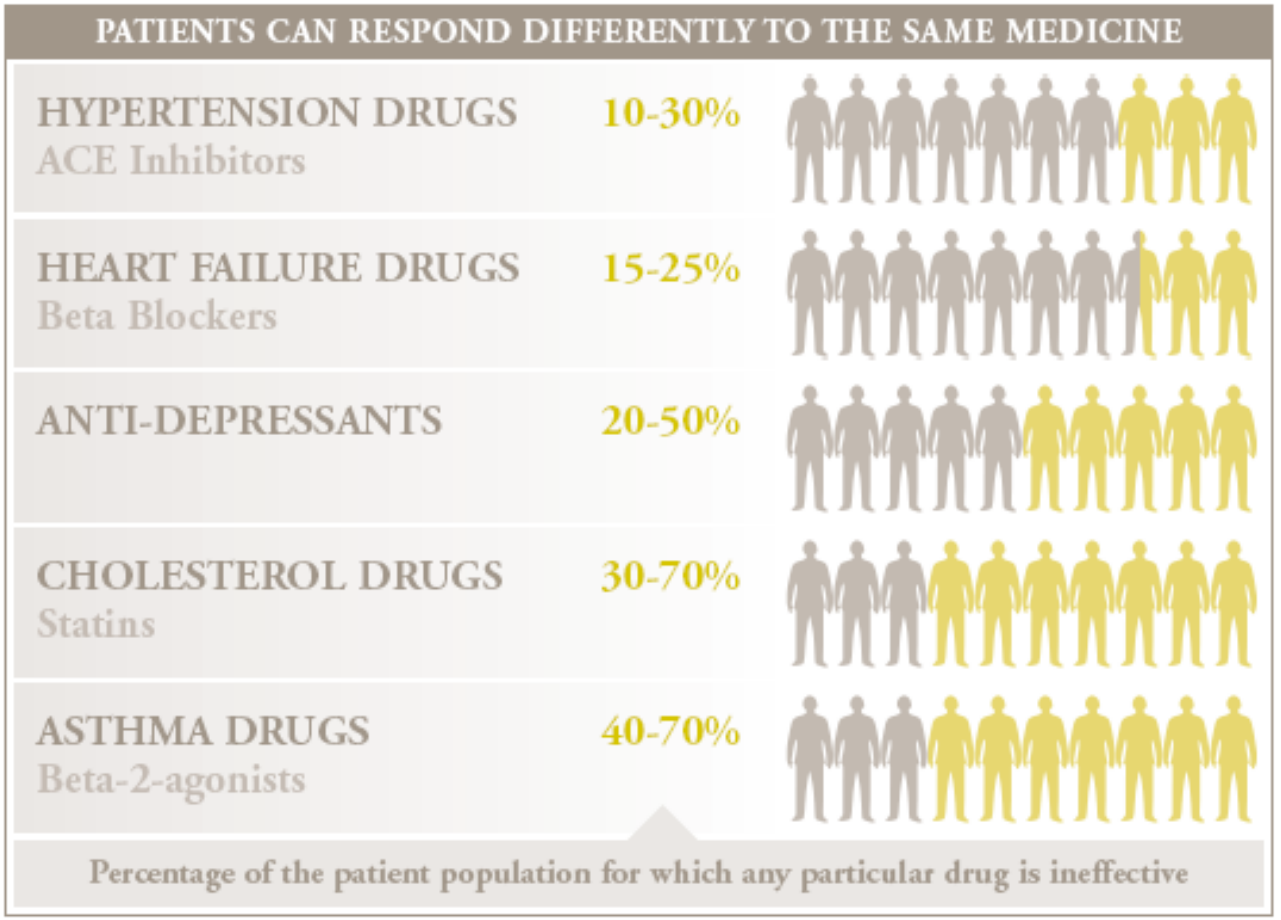
Definitions

- the branch of genetics that studies the genetically determined variations in responses to drugs (wordnetweb.princeton.edu/perl/webwn)
- The study of genetic variation that gives rise to differing responses to drugs (en.wiktionary.org/wiki/pharmacogenetics)
- the study of the role of inheritance in the individual variation in drug response (www.etsu.edu/com/genomics/omics/somedefinitions.aspx)
- The study of how different groups of people respond to drugs, based on their genetic makeup (www.gsk-clinicalstudyregister.com/glossary3.jsp)

Variable Response to Drugs



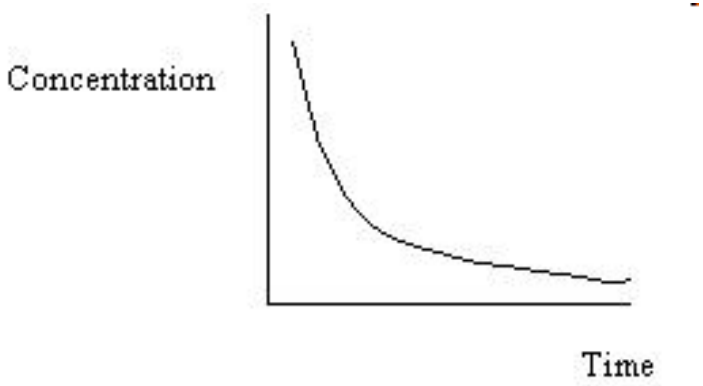
Personalized Medicine Coalition: Case for Personalized Medicine

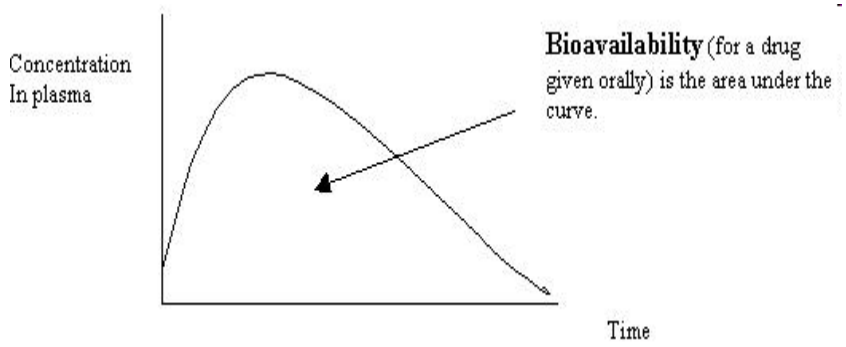
Partial list of Pharmacogenetic tests

Gene	Drug Metabolized
CCR5	Maraviroc (Selzentry)
CYP2C9 and *VKORC1*	Warfarin (Coumadin)
CYP2C19	Voriconazole (Vfend®)
CYP2D6	Atomoxetine (Strattera)
CYP2D6	Tamoxifen (Nolvadex)
DPYD	Capecitabine (Xeloda®)
*HLA-B*5701*	Abacavir (Ziagen)
*HLA-B*1502*	Carbamazepine (Tegretol®)
*HLA-B*5801*	Allopurinol
*HLA-DRB1*01*	Nevirapine (Viramune)
*HLA-DRB1*07*	Ximelagatran
TPMT	Azathioprine (Imuran®)
UGT1A1	Irinotecan (Camptosar®)

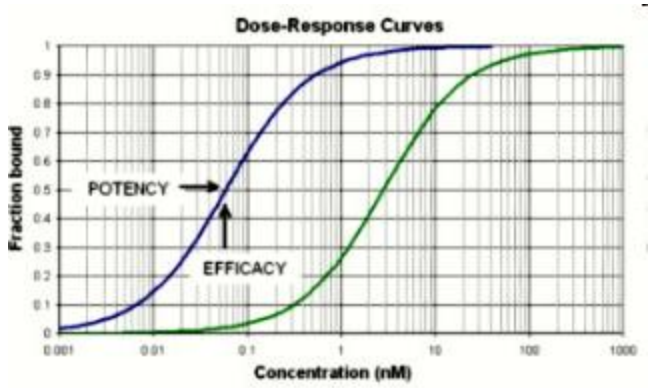
***Pratt VM**, Dunn ST, Weck KE. Personalized Medicine: The Role of Laboratories. Update Magazine, 2008.*

- **Pharmacokinetics** is the study of what the body does to a drug.





- **Pharmacodynamics** is the study of what a drug does to the body.



http://www.4um.com/tutorial/science/pharmak.htm

Adverse Drug Reactions (ADRs)

- 6-7% of hospitalizations
- ~100,000 deaths/year (4th leading cause of death)
- Termination of ~20% of drug candidates under development

Pharmacogenomics

- Constitutional/inherited variants
  - Cytochrome P450s (2D6, 2C19, 2C9)
  - *VKORC1*
  - *UGT1A1*
  - *G6PD*
  - HLA
- Somatic/tumor-specific variants
  - *KRAS*
  - *BCR/ABL*
  - *EGFR* pathway
  - *cKIT*
  - *BRAF*
  - *ALK*
- Infectious Agents
  - HIV
  - HCV

Companion Diagnostic

- Where the drug and pharmacogenetic test are approved by the FDA about the same time.

  Submitted together for test and drug co-approval

Inherited/Constitutional variants

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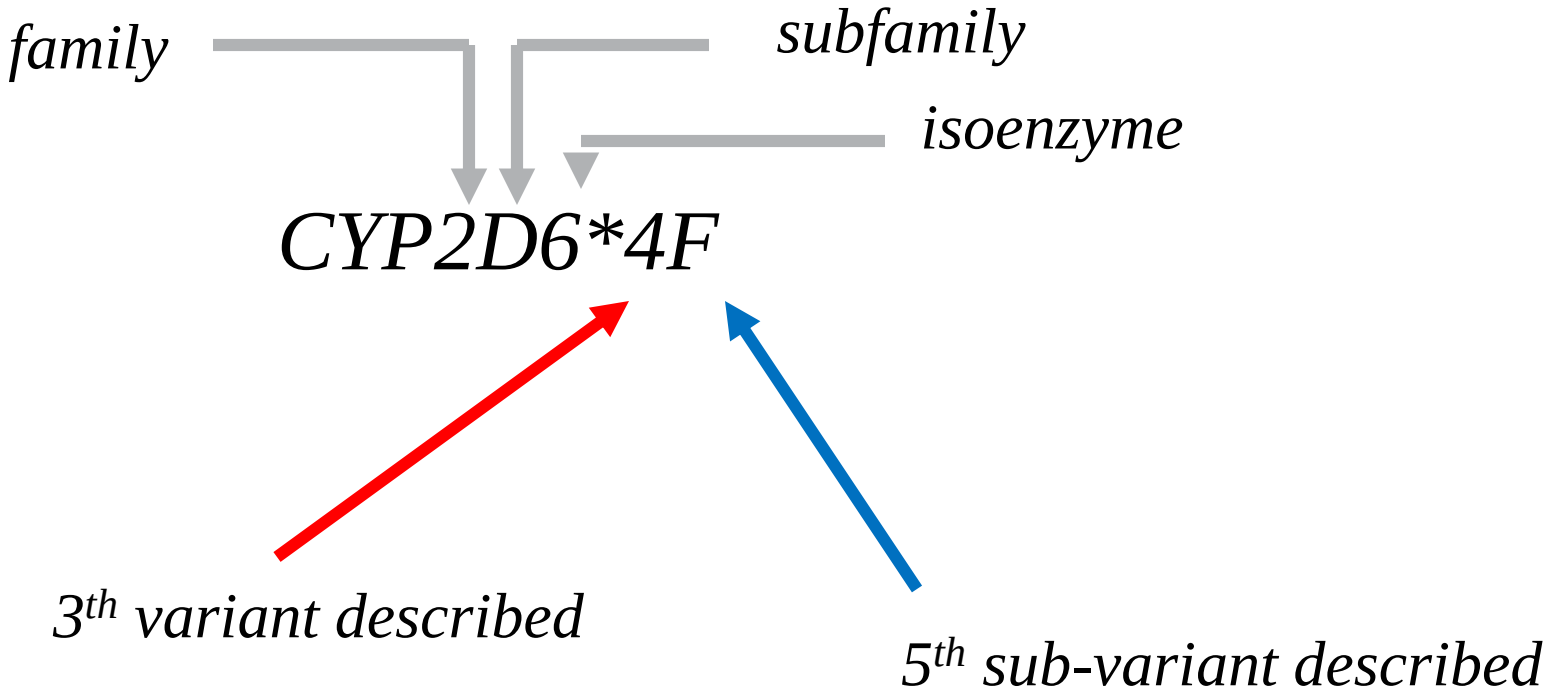
CYP450

- Enzyme family
- Predominantly in liver
- Involved in toxin/drug metabolism

CYP450 Nomenclature

- *1 = normal allele (no mutation detected)
- *alleles numbered in order of description
- Sub-alleles alphabetized in order of description
- Website: http://www.cypalleles.ki.se/

CYP450 Nomenclature



CYP2D6*4 example

*4A	100C>T; 974C>A; 984A>G; 997C>G; 1661G>C; **1846G>A**; 4180G>C
*4B	100C>T; 974C>A; 984A>G; 997C>G; **1846G>A**; 4180G>C
*4C	100C>T; 1661G>C; **1846G>A**; 3887T>C; 4180G>C
*4D	100C>T; 1039C>T; 1661G>C; **1846G>A**; 4180G>C
*4E	100C>T; 1661G>C; **1846G>A**; 4180G>C
*4F	100C>T; 974C>A; 984A>G; 997C>G; 1661G>C; **1846G>A**; 1858C>T; 4180G>C
*4G	100C>T; 974C>A; 984A>G; 997C>G; 1661G>C; **1846G>A**; 2938C>T; 4180G>C
*4H	100C>T; 974C>A; 984A>G; 997C>G; 1661G>C; **1846G>A**; 3877G>C; 4180G>C
*4J	100C>T; 974C>A; 984A>G; 997C>G; 1661G>C; **1846G>A**
*4K	100C>T; 1661G>C; **1846G>A**; 2850C>T; 4180G>C
*4L	100C>T; 997C>G; 1661G>C; **1846G>A**; 4180G>C
*4M	-1235A>G; 746C>G; 843T>G 974C>A; 984A>G; 997C>G; 1661G>C; **1846G>A**; 2097A>G; 3384A>C; 3582A>G; 4401C>T

http://www.cypalleles.ki.se/cyp2d6.htm

CYP allele definition - function

- Normal
- Decreased
- No function
- Increased
- Unknown function
- Uncertain function

https://cpicpgx.org/

CYP phenotype – Metabolizer status

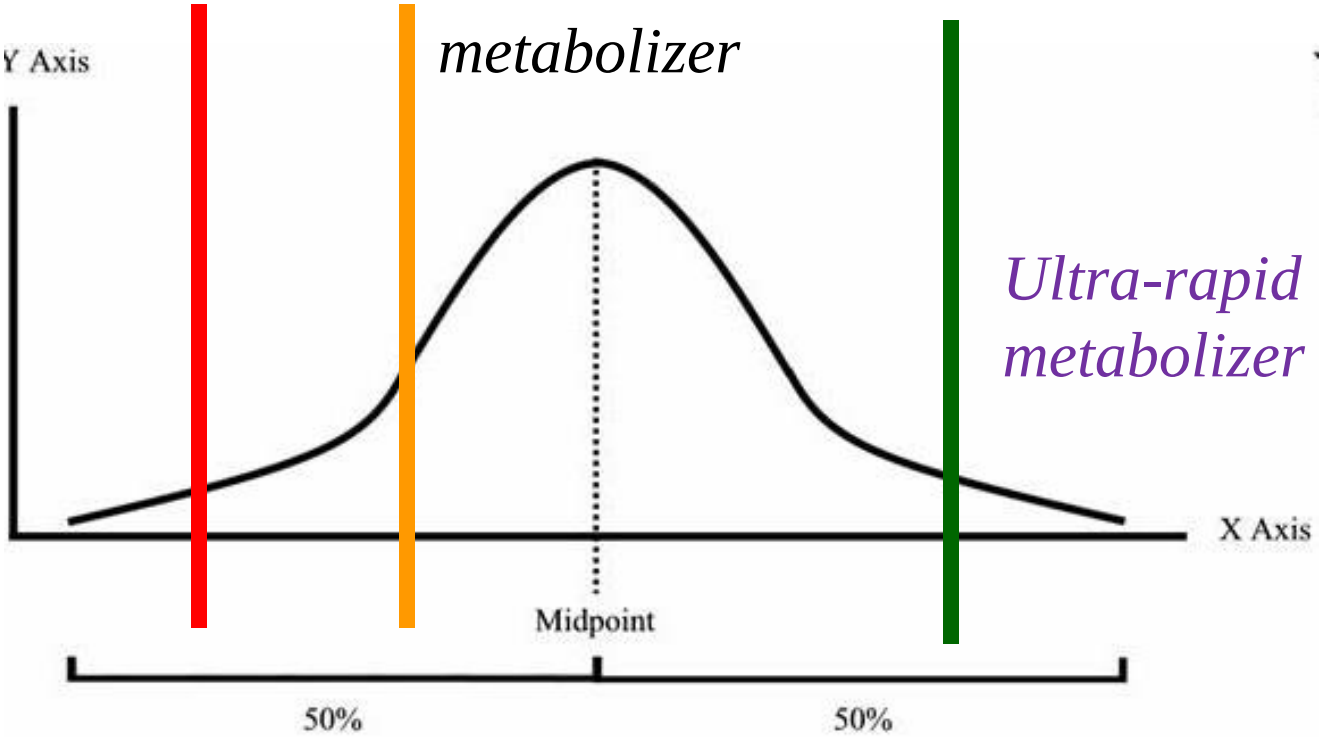
- Normal Metabolizer (EM)
  2 functional alleles
- Reduced Metabolizer (IM)
  1 decreased function allele
  1 no function allele
- Poor Metabolizer (PM)
  2 no function alleles
- Rapid Metabolizer (RM)
  1 increased function allele
- Ultra-rapid metabolizer (UM)
  >1 increased function allele

Normal Distribution

Normal metabolizer

Poor metabolizer

Ultra-rapid metabolizer



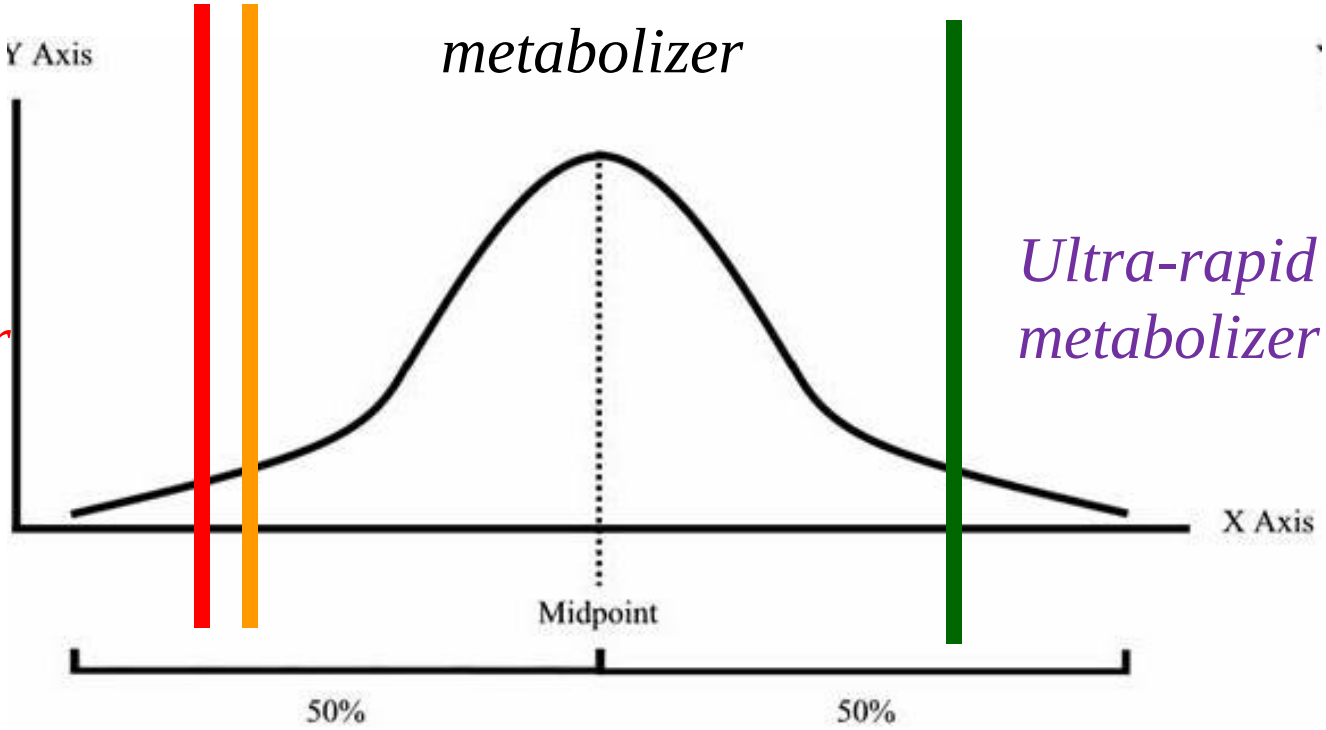
Reduced metabolizer

Normal Distribution

Normal metabolizer

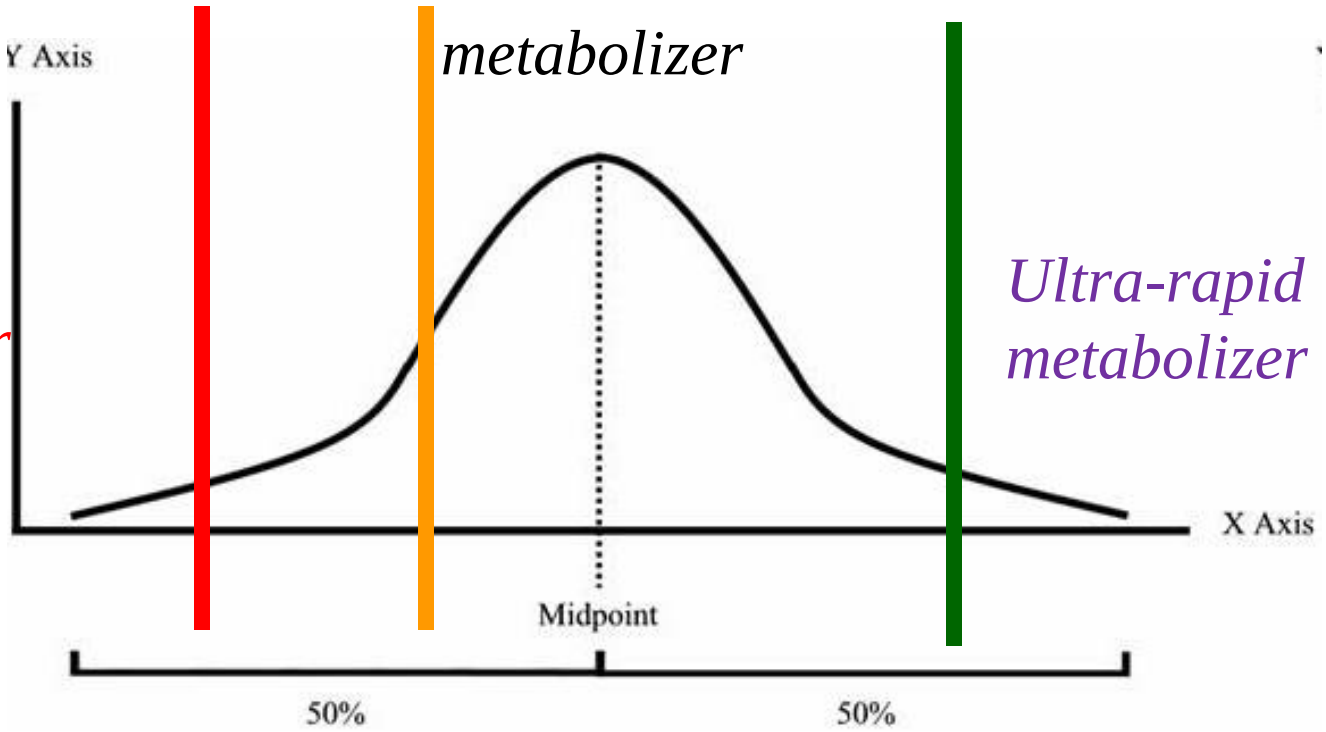
Poor metabolizer

Ultra-rapid metabolizer



Reduced metabolizer

Normal Distribution



Certain non-drugs can cause affect CYP metabolism

- Grapefruit (juice) inhibits CYP3A4

+

- Broccoli induces CYP1A2

- St. John's wort induces CYP3A4

http://pested.ifas.ufl.edu/newsletters/2009-01/Pesticide_Potpourri.htm

http://happyhealthybalance.blogspot.com/2009/12/eat-more-broccoli.html

http://www.nlm.nih.gov/medlineplus/ency/imagepages/19329.htm

http://en.wikipedia.org/wiki/St_John%27s_wort

CYP2D6

- Chromosome 22
- More than 100 alleles described
- Estimated to metabolize 25% of all drugs
- PMs

  Caucasians: 5-10%

CYP2D6

- Metabolizes
  - Tamoxifen
  - Antidepressants
    - Fluoxetine (Prozac)
  - Pain management
    - Codeine (CPIC Guidelines)
  - Antipsychotics
- Inhibitors
  - Bupropion (Wellbutrin)
  - Fluoxetine (Prozac)
  - Paroxetine (Paxil)

http://medicine.iupui.edu/clinpharm/ddis/

Example: Codeine

- Codeine is used in the treatment
  - Pain
  - Cough
  - Diarrhea
- Risk cannot be ruled out during pregnancy.
- The drug has a currently accepted medical use in treatment in the US or a currently accepted medical use with severe restrictions.
- Abuse of the drug may lead to severe psychological or physical dependence.

http://www.drugs.com/imprints/54-783-9981.html

Codeine

- Metabolized by CYP2D6 to more active form → morphine
- CPIC Guidelines

FDA Postmarket Drug Safety Information for Patients and Providers ***Use of Codeine Products in Nursing Mothers***

U.S. Department of Health & Human Services www.hhs.gov

U.S. Food and Drug Administration

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Drug Safety and Availability

Postmarket Drug Safety Information for Patients and

Use of Codeine Products in Nursing Mothers - Questions and Answers

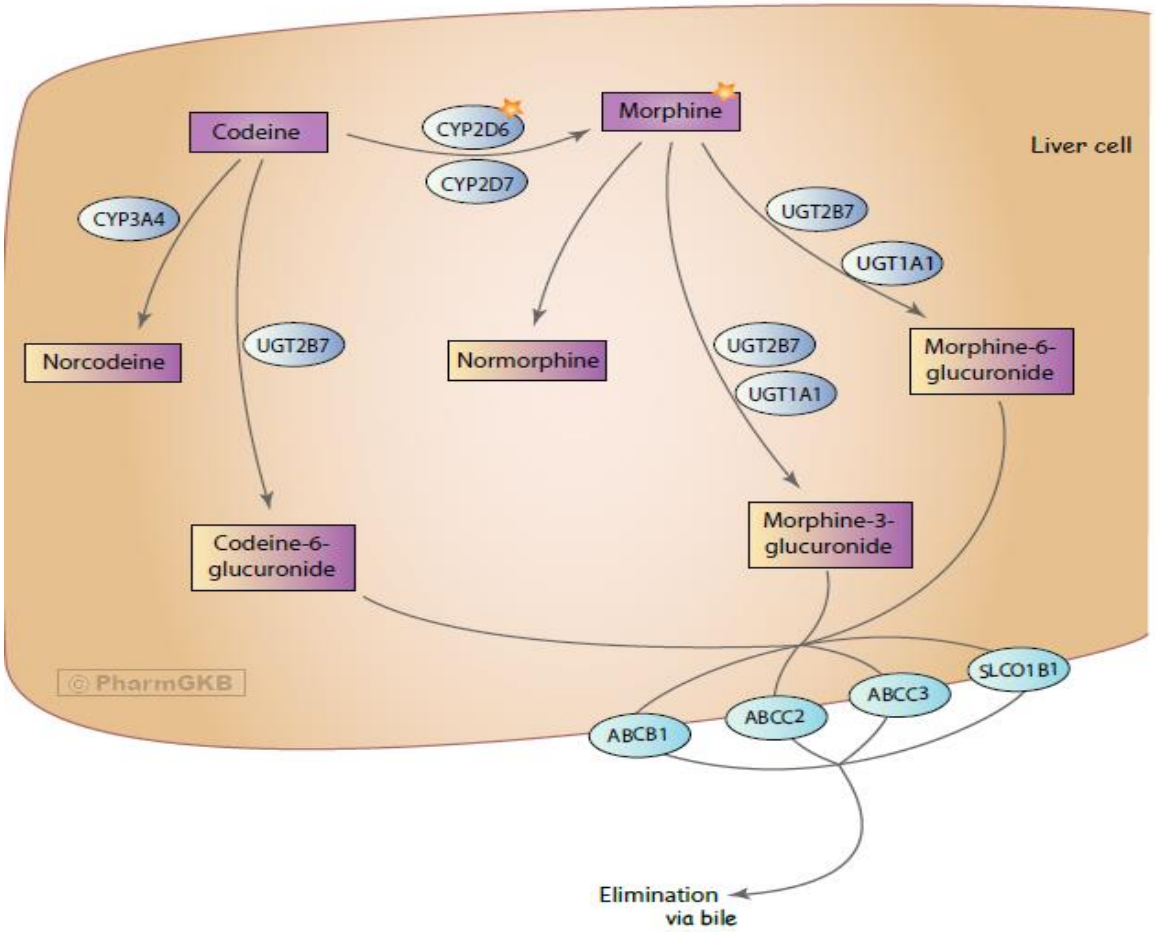
8/2007

Table 1: Approximate number of ultra-rapid metabolizers of codeine in different populations

Population	Ultra-rapid metabolizers (per 100 people)
Caucasians	1-10
African Americans	3
Chinese Japanese	1
Hispanics	1
North Africans Ethiopians Saudi Arabians	16-28

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118113.htm

Codeine Metabolism Pathway



https://www.pharmgkb.org/pathway/PA146123006

Codeine dosing

- IMs

  Consider increased dose; if no pain relief consider and alternate analgesics

- PMs

  Avoid codeine and tramadol

- UMs

  Avoid codeine and tramadol

https://www.pharmgkb.org/drug/PA449088

CPIC Guidelines for Codeine

Likely phenotype*	Activity score	Genotypes	Examples of genotypes	Implications for codeine metabolism	Recommendations for codeine therapy
Ultrarapid metabolizer (~1-2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopiod. Consider avoiding tramadol.
Normal metabolizer (~77-92% of patients)	1.0-2.0**	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10	Normal morphine formation	15-50 mg every 4h as needed for pain (label recommendation)
Reduced metabolizer (~2-11% of patients)	0.5**	An individual carrying one reduced and one nonfunctional allele	*4/*10, *5/*41	Reduced morphine formation	Begin with 15-60 mg every 4h as needed for pain. If no response, consider alternative analgesics such as morphine or a nonopiod. Monitor tramadol use for response.
Poor metabolizer (~5-10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopiod. Consider avoiding tramadol.

Various Assays/Platforms for *CYP2D6*

Platform	Legal Status
Autogenomics INFINITI™	FDA-cleared
Luminex xTag™	FDA-cleared
Agena (formerly Sequenom)	RUO*
LifeTech (Fisher)	LDT
Affymetrix	RUO*

**RUO = Research Use Only*
***IUO = Investigational Use Only*

CYP2C19

- Chromosome 10
- More than 25 alleles described
- PMs

  Caucasians: 3-5%

  Asians: 15-20%

CYP2C19

- Metabolizes
  - Proton Pump Inhibitors
    - Omeprazole (Prilosec)
  - Antidepressants
    - amitriptyline
    - Citalopram/escitalopram
    - clomipramine
  - Clopidogrel (Plavix) (CPIC Guidelines)

Predicted metabolizer phenotypes based on *CYP2C19* genotype

	Predicted Metabolizer Phenotype (Average Multi-Ethnic Frequency[1])								
Allele	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***17***
1	EM (35-50%)	IM (17-35%)	IM (1-11%)	IM (<1%)	IM (<1%)	IM (<1%)	IM (<1%)	IM (<1%)	UM (3-27%)
2		PM (2-8%)	PM (0-5%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (1-6%)
3			PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
4				PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
5					PM (<1%)	PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
6						PM (<1%)	PM (<1%)	PM (<1%)	IM[2] (<1%)
7							PM (<1%)	PM (<1%)	IM[2] (<1%)
8								PM (<1%)	IM[2] (<1%)
17									UM (1-5%)

CPIC Guidelines, supplemental information

Example: Clopidogrel (Plavix®)

- inhibit blood clots in coronary artery disease, peripheral artery disease, and cerebrovascular disease.
- Metabolized by cytochrome CYP2C19 to active form

  2-{1-[1-(2-chlorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanyl-3-piperidinylidene}acetic acid
- FDA announced that clopidogrel cannot be taken with Prilosec (omeprazole) and Nexium (esomeprazole)

  Inhibitors of 2C19

http://www.drugs.com/plavix-images.html

Clopidogrel use

- Prevention of vascular ischemic events in patients with symptomatic atherosclerosis
- Acute coronary syndrome without ST-segment elevation (NSTEMI)
- ST elevation MI (STEMI)
- It is also used, along with aspirin, for the prevention of thrombosis after placement of intracoronary stent

FDA changed Plavix Label

- 12 March 2010

  Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.

  Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.

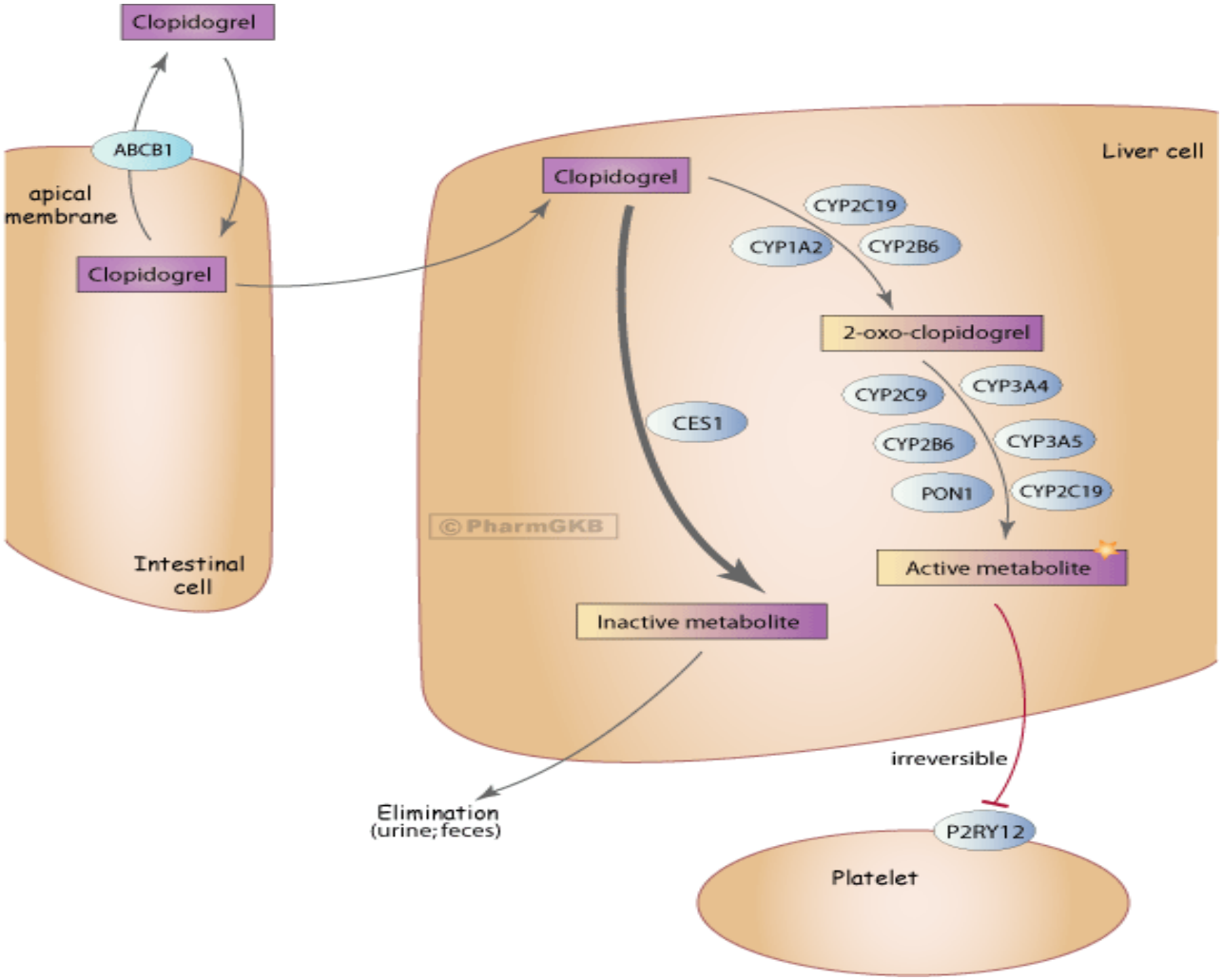
  Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

- Updated: 10/03/2016

  The FDA-approved drug label for clopidogrel (Plavix) warns that patients who are CYP2C19 poor metabolizers may have diminished effectiveness of the drug as compared to patients with normal CYP2C19 function. The drug label suggests that a different platelet P2Y12 inhibitor be used in patients identified as CYP2C19 poor metabolizers.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm

Clopidogrel Metabolism Pathway



http://www.pharmgkb.org/pathway/PA154424674#

Clopidogrel dosing

- IMs

  Prasugrel, ticagrelor or other alternative therapy (if no contraindication)

- PMs

  Prasugrel, ticagrelor or other alternative therapy (if no contraindication)

- UMs

  Clopidogrel label-recommended dosage and administration

http://www.pharmgkb.org/drug/PA449053

CPIC Guidelines for Clopidogrel

Likely phenotype	Genotypes	Examples of genotypes	Implications for clopidogrel	Therapeutic recommendations
Ultrarapid metabolizer (UM) (~5-30% of patients)	An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased activity allele (*17)	*1/*17, *17/*17	Increased platelet inhibition; decreased residual platelet aggregation [1]	Clopidogrel - label recommended dosage and administration
Extensive metabolizer (EM) (~35-50% of patients)	An individual carrying two functional (*1) alleles	*1/*1	Normal platelet inhibition; normal residual platelet aggregation	Clopidogrel - label recommended dosage and administration
Intermediate metabolizer (IM) (~18-45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2-*8) or one loss-of-function allele (*2-*8) plus one increased activity allele (*17) [2]	*1/*2, *1/*3, *2/*17	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor
Poor metabolizer (PM) (~2-15% of patients)	An individual carrying two loss-of-function alleles (*2-*8)	*2/*2, *2/*3, *3/*3	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor

Various Assays/Platforms for *CYP2C19*

Platform	Legal Status
Affymetrix	RUO*
Agena	RUO*
Autogenomics INFINITI™	FDA-cleared
GenMark eSensor	RUO*
Luminex xTag™	FDA-cleared
LifeTech (Fisher)	LDT
Nanosphere Verigene	FDA-cleared
Spartan Bioscience	FDA-cleared
VerifyNow P2Y12 Test**	FDA-cleared

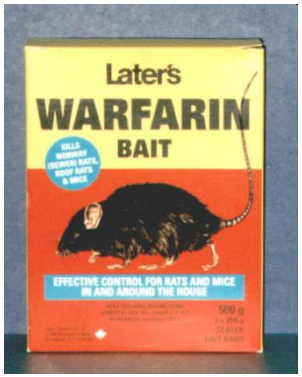
**RUO = Investigational Use Only*
***Platelet function assay*

Alleles tested by each platform

Platform	Affymetrix DMET	Agena Biosciences (Sequenom) iPLEX ADME	Autogenomics INFINITI	GenMark eSensor	Luminex xTAG	LifeTech Taqman	Nanosphere Verigene	Spartan Bioscience
Alleles tested	*2A, *2B, *3, *4, *5, *6, *7, *8, *9, *10, *12, *13, *14, *15, *17, 439FS, 241FS, V331I	*1B, *2, *3, *4, *5A, *5B, *6, *7, *8, *12, *17	*2, *3, *17	*2, *3, *4, *5, *6, *7, *8, *9, *10, *13, *17	*2, *3, *4, *5, *6, *7, *8, *9, *10, *17	*2, *3, *4, *4B, *6, *8, *17 (custom)	*2, *3, *17	*2, *3, *17

Example: Warfarin (Coumadin®)

- Named for the Wisconsin Alumni Research Foundation (WARF) that patented it
- Originally marketed as rat poison
- 1951, a military recruit attempted suicide
  research in anticoagulation properties
- Prescribed more 30M times in the US each year
- Accounts for over 43,000 ER visits each year
- 2 genes associated with 40% of variability in drug response
  CYP2C9
  VKORC1



http://www.ch.ic.ac.uk/local/projects/McIntosh/MainFrame.html

Warfarin Dosing

- www.Warfarindosing.org
- Individual dosing of Warfarin
  - Genotype
    - *VKORC1*
    - *CYP2C9*
  - Weight
  - Height
  - Age
  - Other interacting drugs
- Monitor with PT (prothrombin time)/INR (International Normalized Ratio)
  - 2.0-3.0
  - Risk for bleeding when ≥4.0

http://www.timc.com.hk/products.html

Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1*

***VKORC1* Genotype (-1639G>A, rs9923231)**	***CYP2C9*1/*1**	***CYP2C9*1/*2**	***CYP2C9*1/*3**	***CYP2C9*2/*2**	***CYP2C9*2/*3**	***CYP2C9*3/*3**
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Reproduced from updated warfarin (Coumadin®) product label

CYP2C9

- Chromosome 10
- More than 35 alleles described
- More commonly SNPs than haplotype

*2 (R144C, c.3608C>T)

- Caucasian frequency: 12.2%

*3 (I359L, c.42614A>C)

- Caucasian frequency: 7.9%

*4 (I359T, c.42615T>C)

*5 (D360E, c.42619C>G)

African American frequency: 1.7%

*6 (10601delA, c.818delA)

African American frequency: 2.7%

VKORC1 (vitamin K1 2,3-epoxide reductase subunit 1)

- In linkage disequilibrium (haplotype)

  -1639G>A

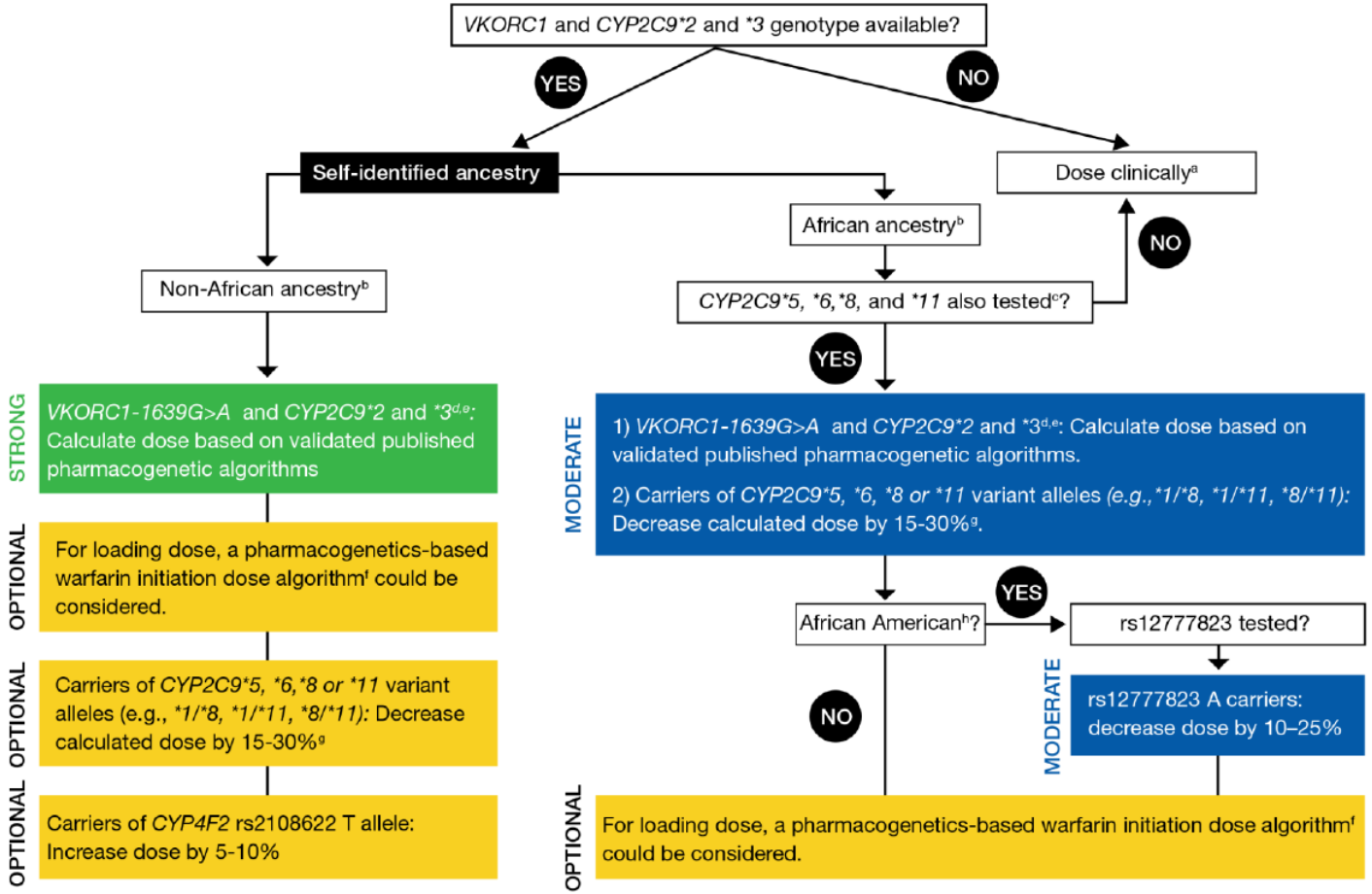
  1173C>T

  1542G>C

  2255T>C

  3730G>A

CPIC Warfarin dosing Algorithm



https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/

Various Assays/Platforms for Warfarin

Platform	Legal Status
Autogenomics INFINITI™	FDA-cleared
Idaho Technologies	Analyte-Specific Reagents
Luminex	IUO**
Nanosphere	FDA-cleared
Osmetech	FDA-cleared
TrimGen	FDA-cleared
LifeTech (Fisher)	LDT
Affymetrix	RUO*
Agena (Sequenom)	RUO*

*RUO = Research Use Only
**IUO = Investigational Use Only

UGT1A1

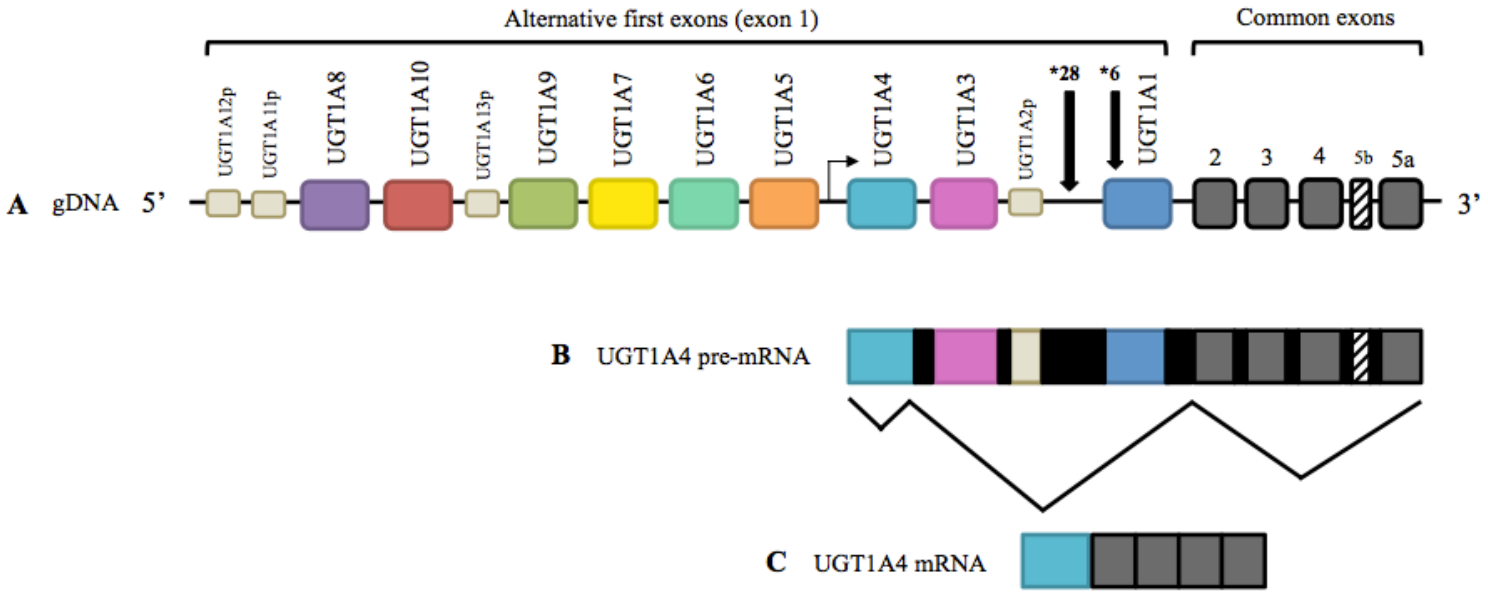
- UDP-glucuronosyltransferase 1A1
- Chromosome 2
- UGT1 complex contains at least 12 promoters/first exons that can be spliced and joined with common exons 2 through 5
- Irinotecan (Camptosar®)

  Metastatic colon cancer
- Atazanavir (EVOTAZ™)

  HIV therapy
- Gene involved in Gilbert syndrome

  hyperbilirubinemia

UGT1A1



https://www.pharmgkb.org/gene/PA420#tabview=tab3&subtab=31

UGT1A1 and irinotecan

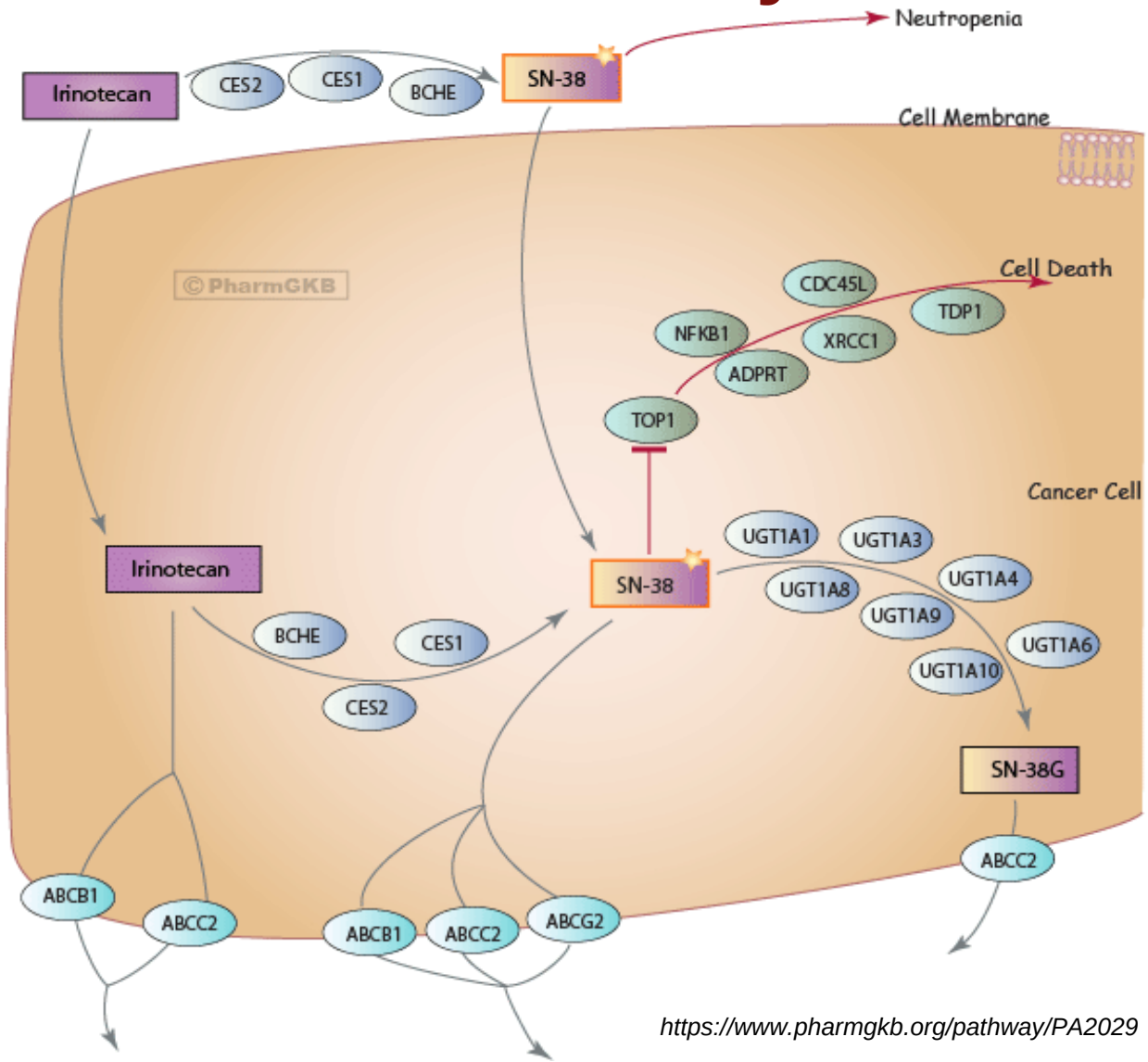
- TA repeat in promoter
- Inactivates active form of irinotecan (SN-38)

  Note: irinotecan is inactive and activated in the body (see pathway)

  Called Phase II metabolism
- *28 (TA_7) metabolizes active irinotecan more slowly

  increased risk for toxicity including high grade neutropenia and/or diarrhea

Irinotecan Pathway



https://www.pharmgkb.org/pathway/PA2029

UGT1A1 Frequency (overall)

- $(TA)_6$ = *1
  - 63%
- $(TA)_7$ = *28
  - 34%
  - Caucasians: 26-31%, African Americans: 42-56%, Asians: 9-16%
- $(TA)_5$ = *36
  - 2%
  - African Americans (3-10%)
- $(TA)_8$ = *37
  - 1%
  - African Americans (2-7%)

http://www.pharmgkb.org/views/reports/loadVariantReport.action?varRptId=129872793

Irinotecan dosing

- *1/*28

  No dosing information

- *28/*28

  Dose >250mg/m^2: reduce initial dose by 30%. Increase dose in response to neutrophil count. Dose <=250mg/m^2: no dose adjustment.

http://www.pharmgkb.org/drug/PA450085

Irinotecan FDA labeling

- When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of Irinotecan Hydrochloride Injection, USP should be considered for patients known to be homozygous for the UGT1A1*28 allele [see Dosage and Administration (2.1) and Warnings and Precautions (5.3)]. However, the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment
- UGT1A1 Testing: A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

http://www.drugs.com/pro/irinotecan.html

Irinotecan dosing decision tree

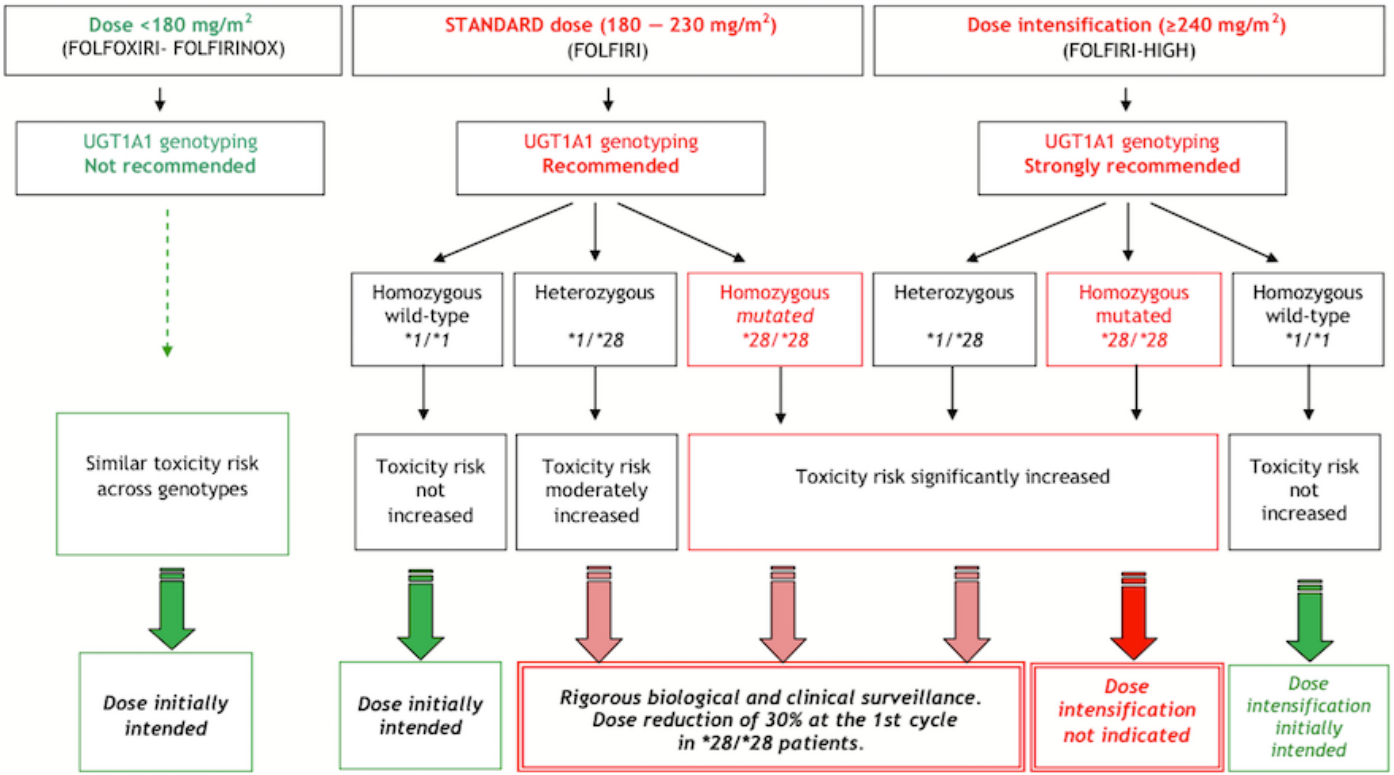


Figure 1 Decision tree for UGT1A1 genotyping depending on initially intended irinotecan dose.

https://www.pharmgkb.org/chemical/PA450085

Various Assays/Platforms for *UGT1A1*

Platform	Legal Status
Hologic/Third Wave	FDA-cleared*
TA repeat analysis and sizing	LDT

**Vendor discontinued assay*

Somatic variants

INDIANA UNIVERSITY

Partial list of Pharmacogenetic tests

Gene	Drug Metabolized
ABL kinase domain	Dasatinib (Sprycel®)
ABL kinase domain	nilotinib (Tasigna™)
ALK	crizotinib (Xalkori®)
BCR/ABL	imatinib mesylate (Gleevec/Glivec)
BRAF	vemurafenib (Zelboraf®)
BRAF	dabrafenib (Tafinlar))
BRAF	trametinib (Mekinist)
ERBB2 (HER2/NEU)	Trastuzumab (Herceptin®)
EGFR	Erlotinib (Tarceva®)
EGFR	gefitinib (Iressa®)
KRAS	Cetuximab (Erbitux®)
KRAS	panitumumab (Vectibix™)

***Pratt VM**, Dunn ST, Weck KE. Personalized Medicine: The Role of Laboratories. Update Magazine, 2008.*

Chronic myeloid leukemia (CML)

- 1960 - Philadelphia chromosome
- 1973 – t(9;22)(q34;q11)
- 1980s - *BCR/ABL1*

  Major breakpoint: p210 (e13a2 [b2a2], e14a2 [b3a2])

  Minor breakpoint: p190 (e1a2)

  Other breakpoint: p230
- 1998 - Imatinib Mesylate

http://www.drugs.com/imprints.php?action=search&drugname=gleevec

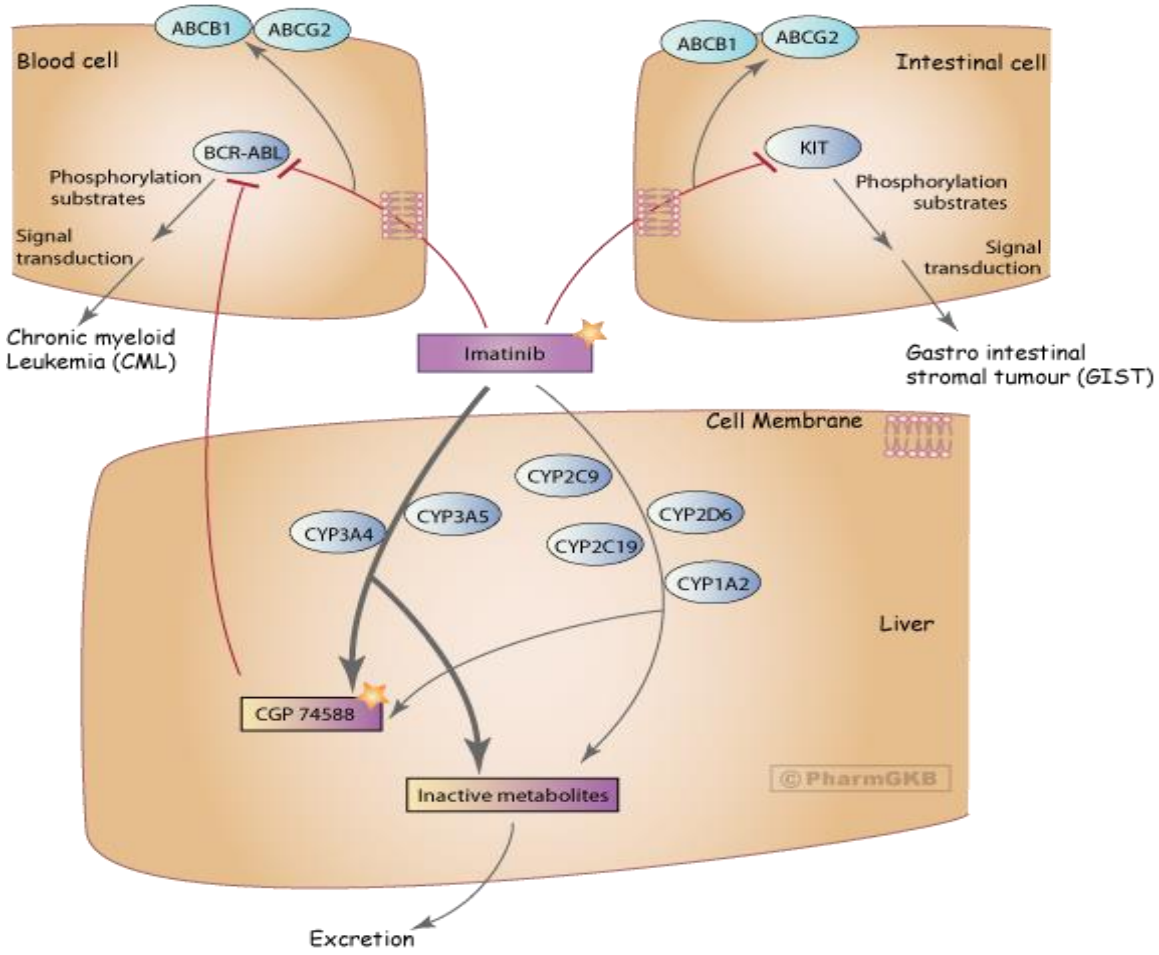
Imatinib Mesylate (Gleevec, Glivec)

- small molecule inhibitor of protein tyrosine kinases
- Primarily metabolized by CYP3A4 and CYP3A5 to an active metabolite, an N-demethylated piperizine derivative
- Treatment for

  CML (chronic myelogenous leukemia); Philadelphia chromosome positive

  Gastrointestinal stromal tumors (GIST) that harbor *KIT* mutations

Imatinib Mesylate Metabolism Pathway



http://www.pharmgkb.org/pathway/PA164713427

Imatinib Mesylate resistance

- Need to sequence *ABL1* kinase domain

  specific single amino acid substitutions, which interfere with binding of the drug to the kinase

  T3151I
- Additional drugs available

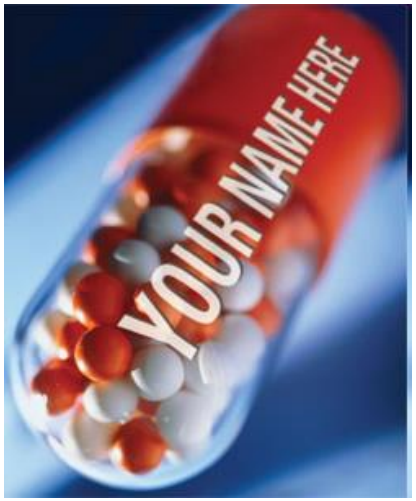
CPIC Guidelines

https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC#

abacavir	CPIC Guideline for abacavir and HLA-B
allopurinol	CPIC Guideline for allopurinol and HLA-B
amitriptyline	CPIC Guideline for amitriptyline and CYP2C19,CYP2D6
atazanavir	CPIC Guideline for atazanavir and UGT1A1
azathioprine	CPIC Guideline for azathioprine and TPMT
capecitabine	CPIC Guideline for capecitabine and DPYD
carbamazepine	CPIC Guideline for carbamazepine and HLA-B
citalopram	CPIC Guideline for citalopram,escitalopram and CYP2C19
clomipramine	CPIC Guideline for clomipramine and CYP2C19,CYP2D6
clopidogrel	CPIC Guideline for clopidogrel and CYP2C19
codeine	CPIC Guideline for codeine and CYP2D6
desipramine	CPIC Guideline for desipramine and CYP2D6
doxepin	CPIC Guideline for doxepin and CYP2C19,CYP2D6
escitalopram	CPIC Guideline for citalopram,escitalopram and CYP2C19
fluorouracil	CPIC Guideline for fluorouracil and DPYD
fluvoxamine	CPIC Guideline for fluvoxamine and CYP2D6
imipramine	CPIC Guideline for imipramine and CYP2C19,CYP2D6
ivacaftor	CPIC Guideline for ivacaftor and CFTR
mercaptopurine	CPIC Guideline for mercaptopurine and TPMT
nortriptyline	CPIC Guideline for nortriptyline and CYP2D6
paroxetine	CPIC Guideline for paroxetine and CYP2D6
peginterferon alfa-2a	CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3
peginterferon alfa-2b	CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3
phenytoin	CPIC Guideline for phenytoin and CYP2C9,HLA-B
rasburicase	CPIC Guideline for rasburicase and G6PD
ribavirin	CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3
sertraline	CPIC Guideline for sertraline and CYP2C19
simvastatin	CPIC Guideline for simvastatin and SLCO1B1
tacrolimus	CPIC Guideline for tacrolimus and CYP3A5
tegafur	CPIC Guideline for tegafur and DPYD
thioguanine	CPIC Guideline for thioguanine and TPMT
trimipramine	CPIC Guideline for trimipramine and CYP2C19,CYP2D6
warfarin	CPIC Guideline for warfarin and CYP2C9,VKORC1

Conclusions

- Pharmacogenetics is a rapidly growing field
- Many variables affect drug metabolism
  - Genotypes
  - Environment
- Genotype/phenotypes correlations are imprecise



http://pganddrugresponse.blogspot.com/2009/03/personalized-medicine-vs-genome-based.html

Questions