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Clinical Meeting & Exhibition

270-L01 – Fitting into Our Genes: Demystifying Pharmacogenomics Tests Using Online Databases

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

- Technical Supervisor for eLab Solutions.

Learning Objectives

- Describe mechanisms of medication interactions and efficacy related to pharmacogenomic variations.
- Contrast and compare various online pharmacogenomics databases.
- Discuss the role of ABC transporters in drug resistance, metabolism, and toxicity.
- Design a medication regimen based on pharmacogenomic test results.

Background

- In the history of healthcare, professionals have used the "one size fits all" approach:
  - Average dose for the population
  - Effective for the large number of people

- Healthcare professionals may change the drug dose based on a patient's:
  - Age, weight, and size
  - Other factors have been considered: organ function, body fat, and blood flow…

Background

- Some studies indicate that the most commonly used pharmaceutical drugs are effective in only 25% to 60% of patients. (1)

- More than 2 million patients have adverse drug reactions (ADRs) in US hospitals each year. (2)
  - Causing at least 100,000 fatalities
  - Costing up to $5.6 million per hospital

(1) Spear, Brian B., Margo Heath-Chiozzi, and Jeffrey Huff. "Clinical application of pharmacogenetics." *Trends in molecular medicine* 7.5 (2001): 201-204.

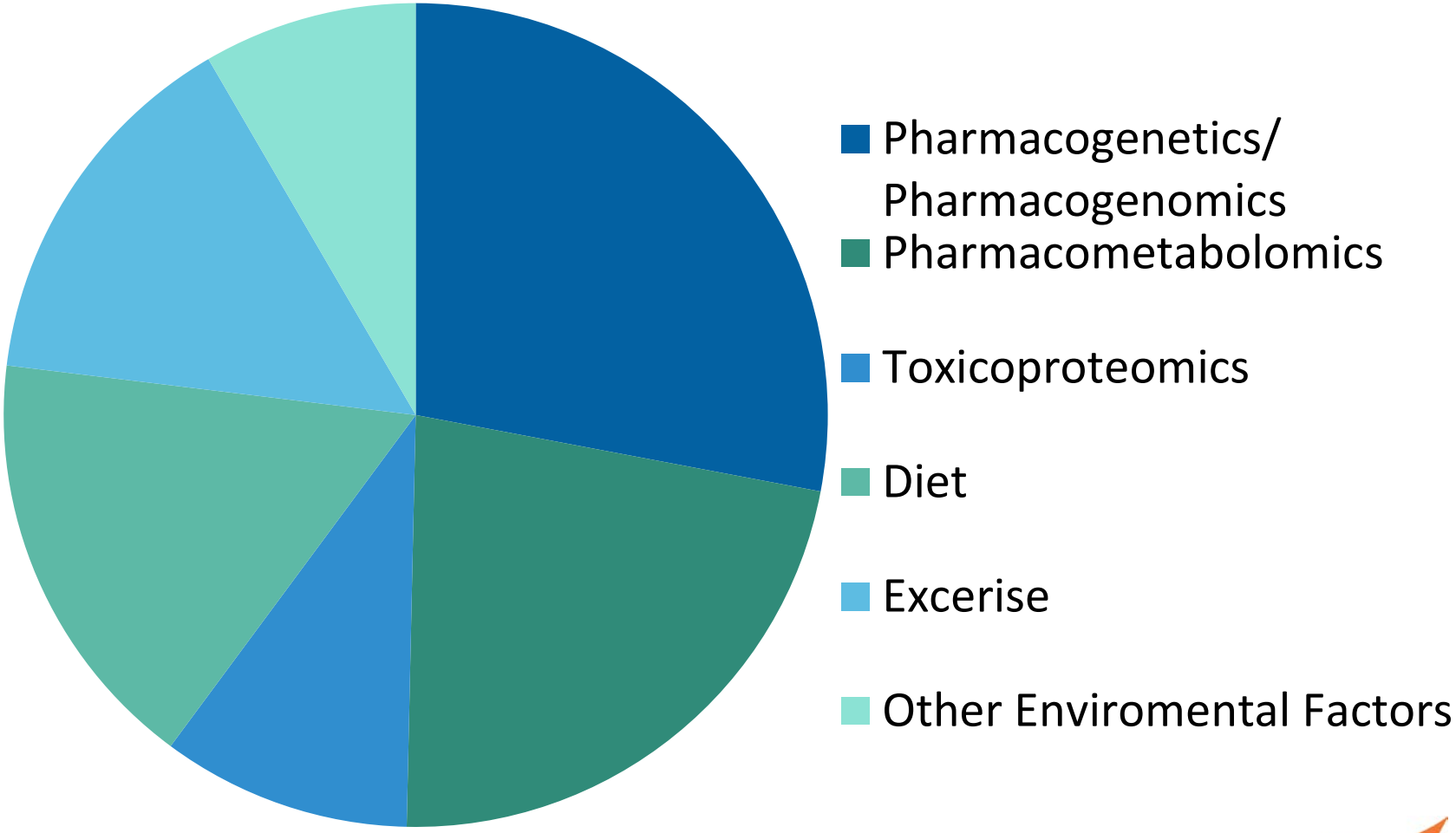
(2) Phillips, Kathryn A., et al. "Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review." *Jama* 286.18 (2001): 2270-2279.

Precision Medicine

- Is a medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient.

- Is able to match the genomic markers to medication that available to the patient.

Precision Medicine



(3) Chambliss, Allison B., and Daniel W. Chan. "Precision medicine: from pharmacogenomics to pharmacoproteomics." *Clinical Proteomics* 13.1 (2016): 25.

Pharmacogenetics vs. Pharmacogenomics

- **Pharmacogenetics (PGt) -** The study of inherited differences or variations in drug metabolism and response.

- **Pharmacogenomics (PGx) -** The study of the role of inheritance in individual variation in drug response. It refers to the general study of the patient's genome to determine drug behavior.

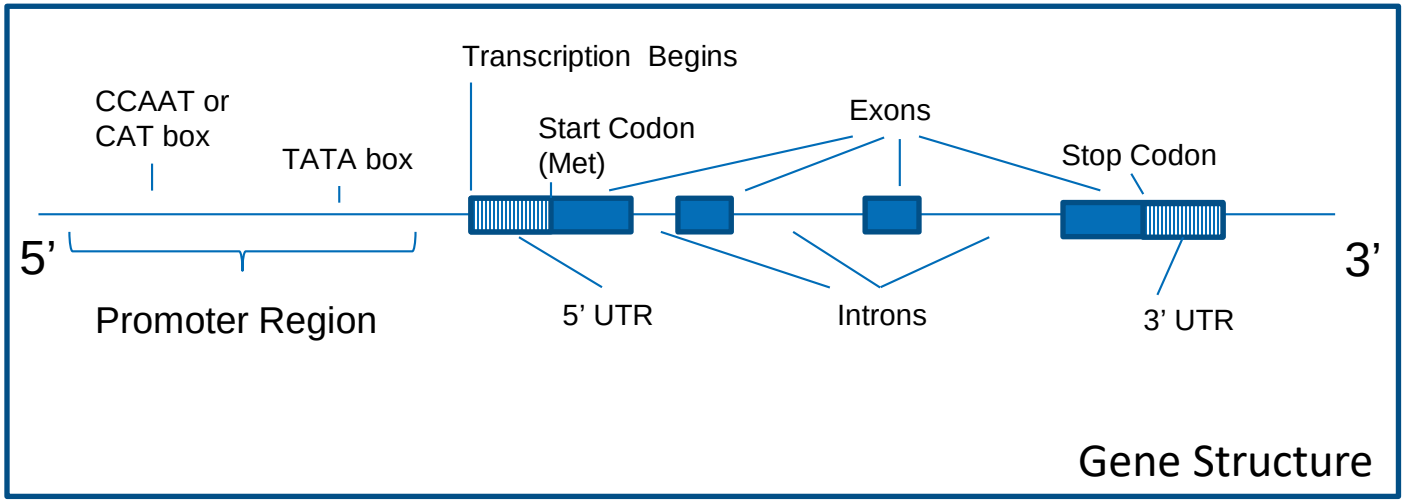
True or False Question

Do the terms pharmacogenomics and precision medicine mean the same thing?

A TRUE

B FALSE

Genetic Variability



(4) Zdanowicz, Martin M. *Concepts in pharmacogenomics*. ASHP, 2010.

Wild Type Allele: Widely accepted sequence for the gene for the majority of the populations

Variant Allele: Alterative sequences for the same gene or different variations at the same genetic locus

Genetic Variability

- Clinical important variant alleles (polymorphisms) in medical genomics are due to:
  - Individuals differ by approximately one nucleotide in every thousand.
    - Single Nucleotide Polymorphisms (SNPs) are single base-pairs substitutions that occur with a frequency of ≥ 1% in a population.
    - Small insertion/deletion in the gene.
  - Insertions, deletions, and duplications (amplification) of bases/genes.

Genetic Variability

- Several different types of SNPs can be found in our DNA where a single nucleotide (thymine, adenine, cytosine, or guanine) is substituted for another nucleotide.
    - Missense variants - the substitution can be a change where the altered codon corresponds to a different amino acid in a specific position in the protein sequence.

	Ala	His	His	Gly	
Wild Type	G C A	C A T	C A T	G G T	
	1046	1047	1048	1049	Codon #
Variant	G C A	C G T	C A T	G G T	
	Ala	Arg	His	Gly	

Genetic Variability

- SNPs (Cont.)
  - Silent variants - the nucleotide substitution does not change in the protein sequence.

	Ala	His	His	Gly	
Wild Type	G C A	C A T	C A T	G G T	
	1046	1047	1048	1049	Codon #
Variant	G C A	C A T	C A T	G G A	
	Ala	His	His	Gly	

  - Nonsense variants - the nucleotide change causes a codon for a specified an amino acid to become a STOP codons (TAA, TAG, or TGA). This results in a premature stop in the protein sequence.

	Arg	Gly	Lys	Phe	
Wild Type	C G G	G G C	A A A	T T T	
	1459	1460	1461	1462	Codon #
Variant	C G G	G G C	T A A	T T T	
	Arg	Gly	Stop (*) or X	Phe	

Genetic Variability Question

- Which of the following variant changes is a nucleotide substitution that alters an amino acid in a specific position in the protein sequence?

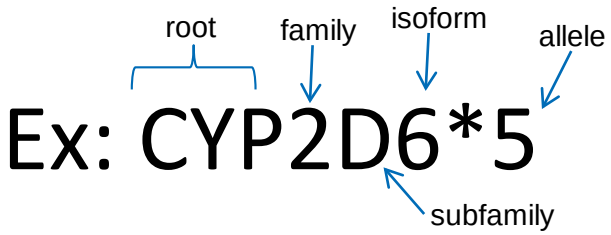
A. Nonsense
B. Silent
C. Missense
D. Frameshift

Nomenclature for Pharmacogenetics

- When discussing the types of genetic variations and polymorphism in PGx, many of the same signs and symbols apply here too:
  - The SNPs and other polymorphisms are given a reference number to identify a specific marker. (rs#). There are 6.5 million known SNPs (rs4680).
  - Many genes follow the system:
    - Root->family->subfamily->gene in subfamily or isoform

    Ex: CYP2D6 or NAT2

    - Allelic variants are distinguished by the * after the gene name.



Example of Genetic Variability

- CYP2D6 is a member of the cytochrome P450 superfamily responsible for playing a major role drug metabolism.
- Encodes for a monoxygenase which is localized to the endoplasmic reticulum.
- Was the first specific human drug metabolic enzyme identified as being polymorphic with over 60 different alleles.
- Known to metabolize as many as 20% of the commonly prescribed drugs.
- Examples of substrates include antidepressants, antipsychotics, antihypertensive, and antiarrhythmics.

Example of Genetic Variability

			Allele Frequency (%)		
Common Allelic Variant	**Alterations**	**Consequences for Enzyme Activity**	**White**	**Black**	**Asian**
CYP2D6*2XN	Gene Duplication	Increased	1-5	2	0-2
CYP2D6*3	Frameshift	Nonfunctional	1-2	0	< 1
CYP2D6*4	Defective Splicing	Nonfunctional	12-21	2-8	< 1
CYP2D6*5	Gene Deletion	Nonfunctional	2-7	6	4-6
CYP2D6*6	Frameshift	Nonfunctional	1	< 1	0
CYP2D6*10	Pro34Ser, Ser486Thr	Decreased	1-2	3-9	38-70
CYP2D6*17	Thr107Ile, Arg29Cys, Ser486Thr	Decreased	< 1	20-35	< 1

- Completely nonfunctional alleles such as CYP2D6*3, *4, *5, and *6 are more commonly seen Caucasians.
- Partially active alleles such as CYP2D6*10 and *17 are seen in African Americans and Asians.
- Ultra-rapid metabolizers are found more frequently among Saudi Arabians (~15-20%) and Ethiopians (~30%).

Example of Genetic Variability

Phenotype	Frequency	Genetic Basis	Implications of 2D6 for Agents Activated
Poor Metabolizer (PM)	~5 to 10%	No functional alleles present	Lack of therapeutic effects may be observed
Intermediate Metabolizer (IM)	~20 to 40%	Either one functional and one mutant/deficient allele or two partially active/deficient alleles present	May show reduced effects
Extensive Metabolizer (EM)	~60 to 80%	Either two active alleles or a combination of one active and one partially active allele present	Should be able to achieve therapeutic effects with normal dosing
Ultra-rapid Metabolizer (UM)	~1 to 5 %	Three or more active alleles present	Increase risk of toxicity; lower dose may be required

Example of Genetic Variability

Example: The analgesic effects of codeine depend on the 2D6-catalyzed biotransformation to morphine.

Safety Flag Raised For Codeine In Kids

by SCOTT HENSLEY

04:38 pm
August 15, 2012

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Enlarge iStockphoto.com

When it comes to pain relief for kids, there may be better options than codeine.

The Food and Drug Administration has warned doctors to be careful with codeine to relieve children's pain.

The agency noted reports of three kids who died and one who almost did after taking codeine following surgery. The kids had their tonsils or adenoids removed to treat obstructive sleep apnea.

Codeine doesn't work to relieve pain until an enzyme in the liver turns some of the drug into morphine. Some people's livers are very efficient at the task, while others don't do a very good job at all.

In the cases cited by the FDA, the children appear to be so-called ultra-rapid metabolizers. Their livers transformed so much codeine into morphine so quickly that they produced a kind of overdose.

Too much morphine can lead to a depression or complete cessation of breathing. That's especially risky for kids who've undergone surgery for sleep apnea.

About 1 to 7 per 100 people are ultra-metabolizers, the FDA said, citing the medical literature. But in some groups, such as Ethiopians, they may run as high as 28 per 100 people. There are tests for the genetic variant involved.

Parents whose children are taking codeine should be on the lookout for "unusual sleepiness, confusion, or difficult or noisy breathing in their child," the FDA said, and get medical help right away if those symptoms appear.

Example of Case

- DS is a 30 year-old woman who gave birth by caesarian section 10 days ago. Her physician prescribed codeine for post-caesarian pain. Despite taking no more than the prescribed dose, DS experienced nausea and dizziness while she was taking codeine. She also noticed that her breastfed infant was lethargic and feeding poorly. When DS mentioned these symptoms to her physician, he recommended that she discontinue codeine use. Within a few days, both DS's and her infant's symptoms were no longer present.

https://www.crediblemeds.org/files/3913/6973/9557/pgx-brochure2011.pdf

Genome Browsers

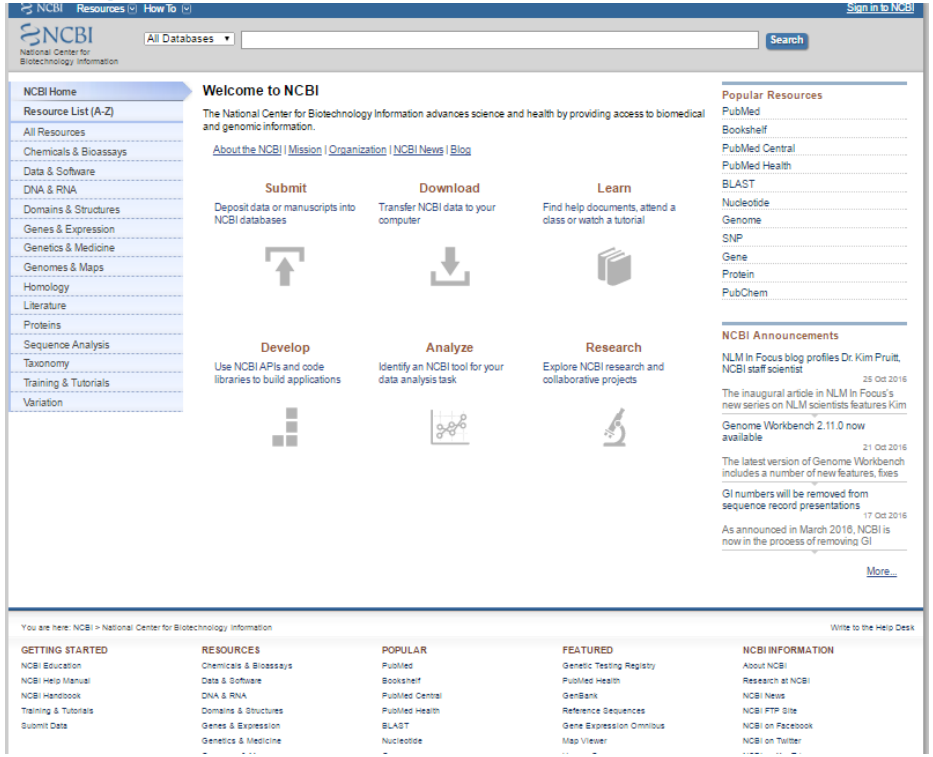
- National Center for Biotechnology Information (NCBI)
- Ensembl
- Santa Cruz Genome Browser: http://genome.ucsc.edu/
- Cancer Genome Browser:
  - http://cancer.sanger.ac.uk/cosmic
  - http://www.cbioportal.org/

National Center for Biotechnology Information (NCBI)

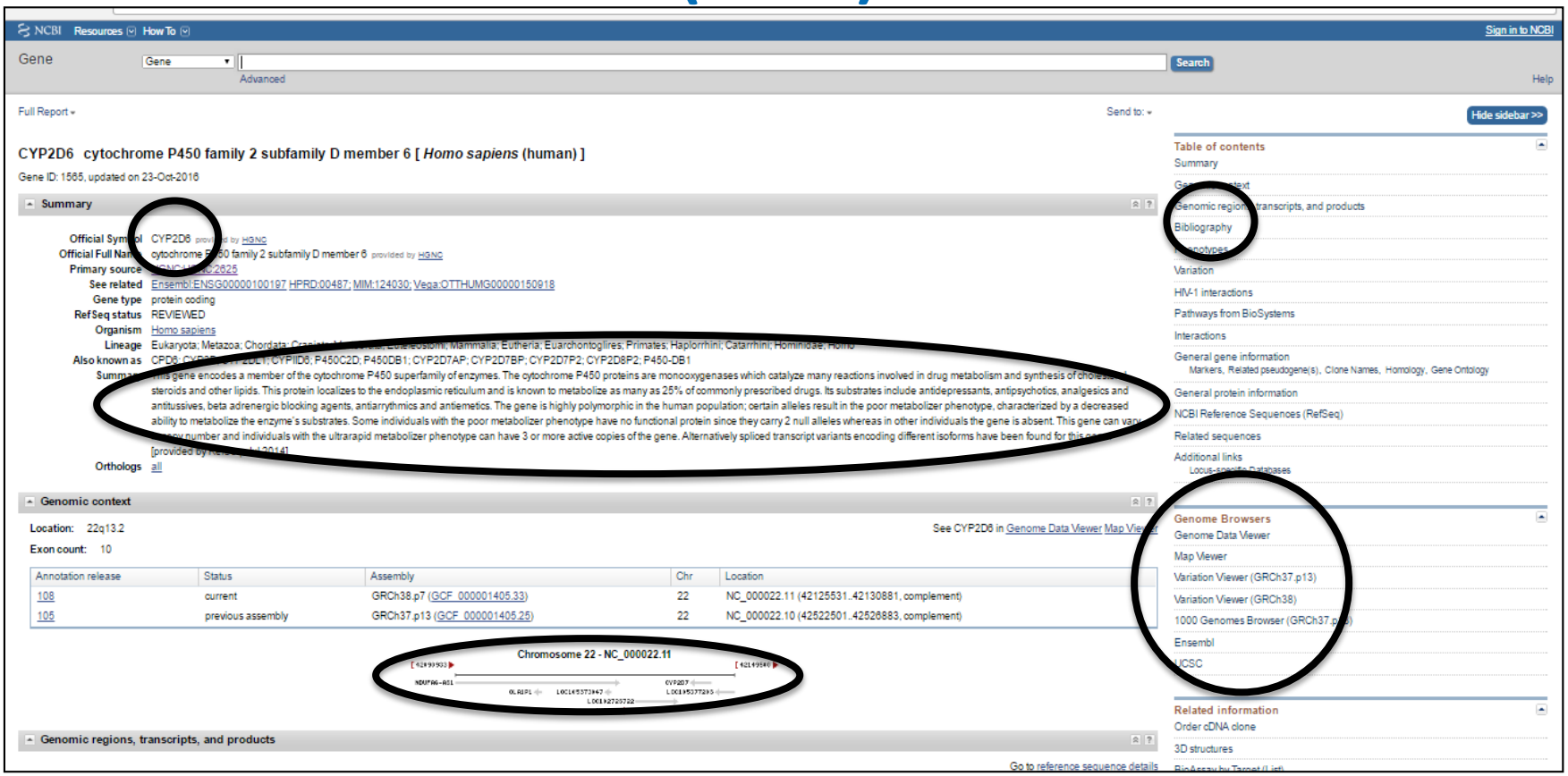
- https://www.ncbi.nlm.nih.gov/

- Created in 1988 to develop information systems for molecular biology.

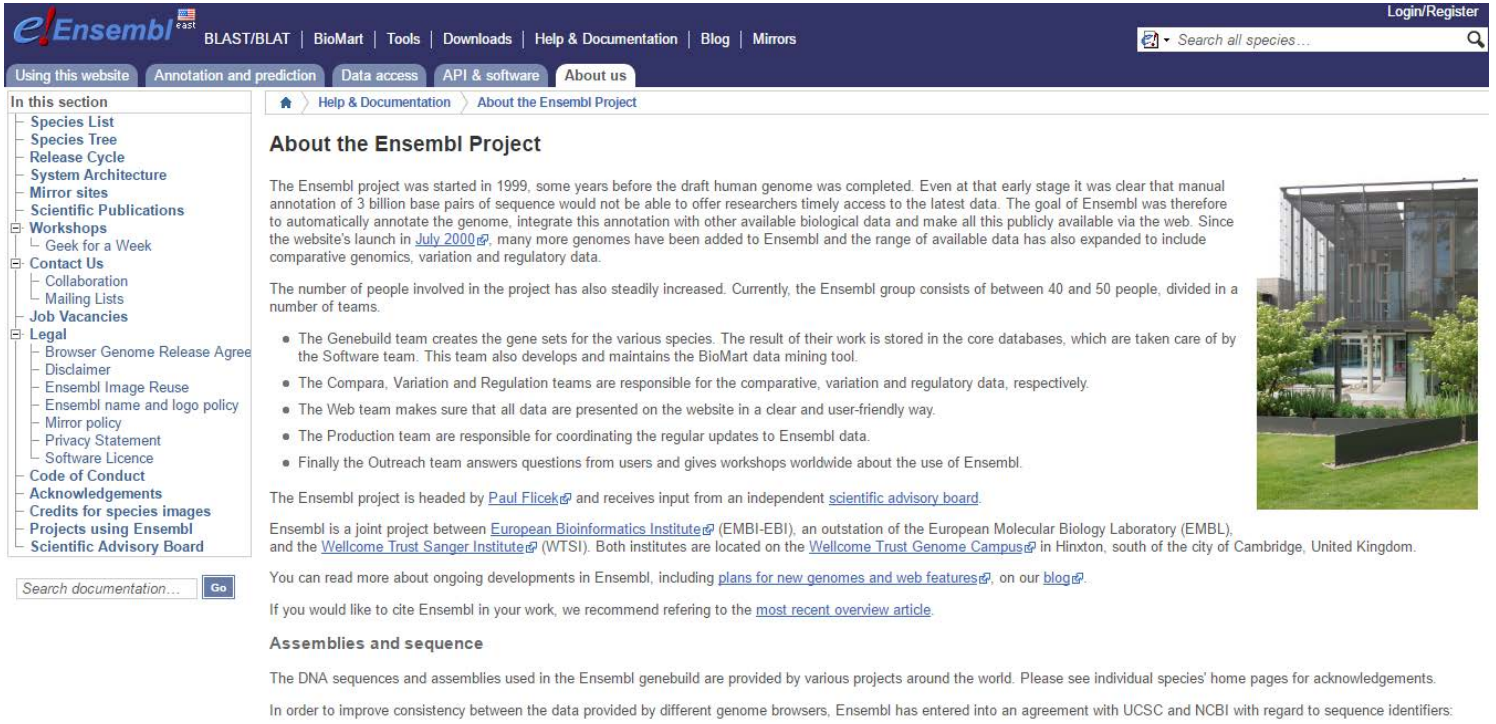
- Many Resources;
  - PubMed Central
  - Gene
  - dbSNP (HapMAP)
  - dbVar
  - Protein Interaction
  - Map Viewer



National Center for Biotechnology Information (NCBI)

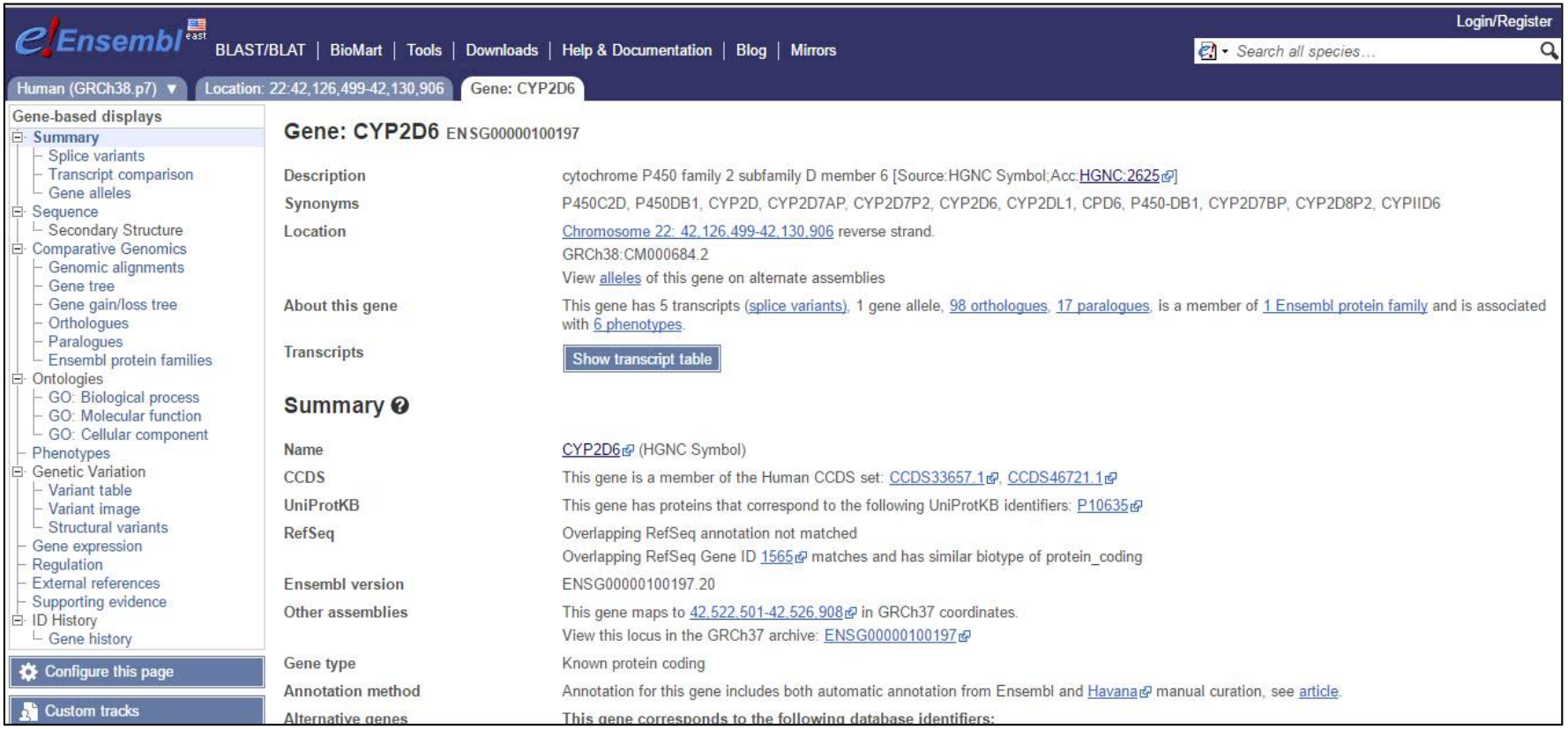


Ensembl Project



- Started in 1999, the website was launched in July of 2000.
- Goal of the project was to annotate the genome from the human genome project as well as integrate other resources.
- www.**ensembl**.org

Ensembl Website



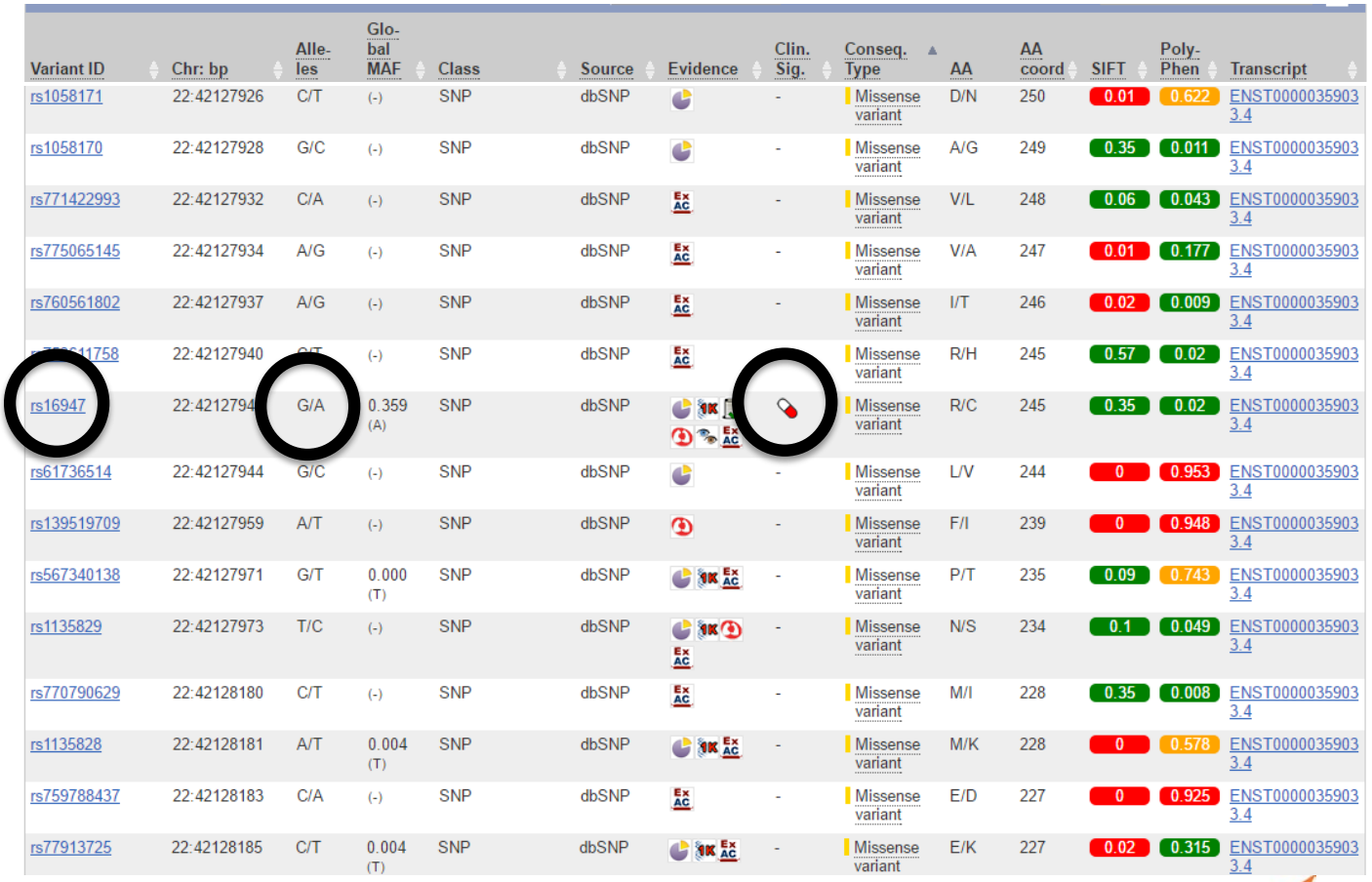
- Genetic Sequence
- Variation Table
  - Frequency (1000 Genomes, ESP, ExAC…)
  - Haplotype Association

Ensembl Website

1) rs# (Variant ID)

2) Variant Change (Allele)

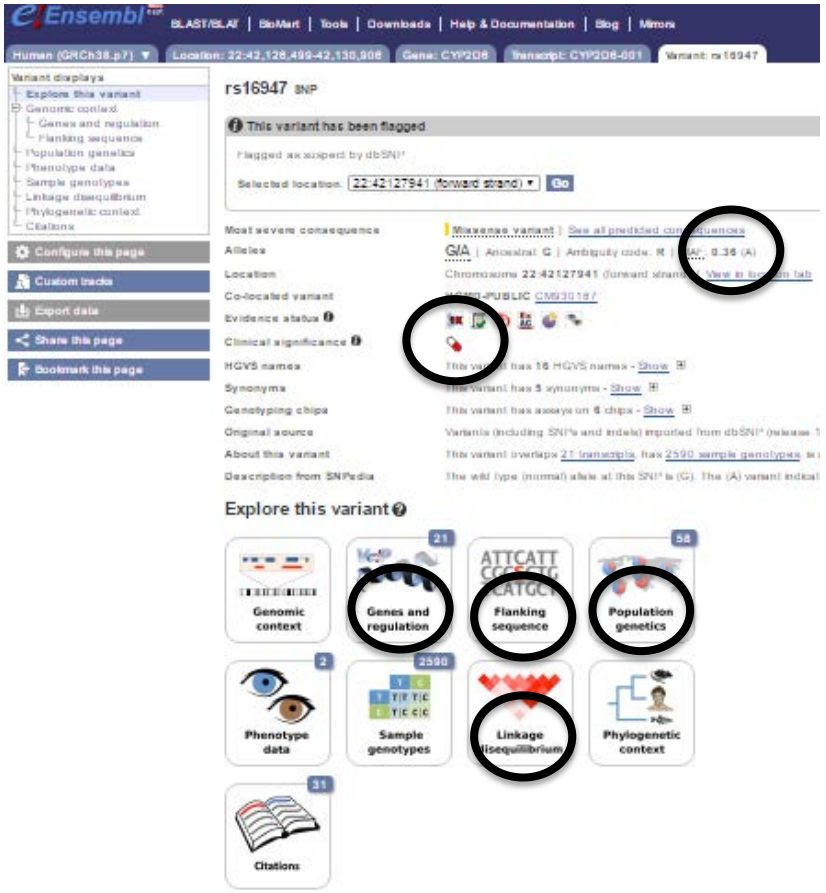
3) Drug Information (Clin. Sig.)



Variant ID	Chr: bp	Alle-les	Glo-bal MAF	Class	Source	Evidence	Clin. Sig.	Conseq. Type	AA	AA coord	SIFT	Poly-Phen	Transcript
rs1058171	22:42127926	C/T	(-)	SNP	dbSNP		-	Missense variant	D/N	250	0.01	0.622	ENST00000359033.4
rs1058170	22:42127928	G/C	(-)	SNP	dbSNP		-	Missense variant	A/G	249	0.35	0.011	ENST00000359033.4
rs771422993	22:42127932	C/A	(-)	SNP	dbSNP		-	Missense variant	V/L	248	0.06	0.043	ENST00000359033.4
rs775065145	22:42127934	A/G	(-)	SNP	dbSNP		-	Missense variant	V/A	247	0.01	0.177	ENST00000359033.4
rs760561802	22:42127937	A/G	(-)	SNP	dbSNP		-	Missense variant	I/T	246	0.02	0.009	ENST00000359033.4
[illegible]1758	22:42127940	[illegible]	(-)	SNP	dbSNP		-	Missense variant	R/H	245	0.57	0.02	ENST00000359033.4
rs16947	22:4212794[illegible]	G/A	0.359 (A)	SNP	dbSNP		-	Missense variant	R/C	245	0.35	0.02	ENST00000359033.4
rs61736514	22:42127944	G/C	(-)	SNP	dbSNP		-	Missense variant	L/V	244	0	0.953	ENST00000359033.4
rs139519709	22:42127959	A/T	(-)	SNP	dbSNP		-	Missense variant	F/I	239	0	0.948	ENST00000359033.4
rs567340138	22:42127971	G/T	0.000 (T)	SNP	dbSNP		-	Missense variant	P/T	235	0.09	0.743	ENST00000359033.4
rs1135829	22:42127973	T/C	(-)	SNP	dbSNP		-	Missense variant	N/S	234	0.1	0.049	ENST00000359033.4
rs770790629	22:42128180	C/T	(-)	SNP	dbSNP		-	Missense variant	M/I	228	0.35	0.008	ENST00000359033.4
rs1135828	22:42128181	A/T	0.004 (T)	SNP	dbSNP		-	Missense variant	M/K	228	0	0.578	ENST00000359033.4
rs759788437	22:42128183	C/A	(-)	SNP	dbSNP		-	Missense variant	E/D	227	0	0.925	ENST00000359033.4
rs77913725	22:42128185	C/T	0.004 (T)	SNP	dbSNP		-	Missense variant	E/K	227	0.02	0.315	ENST00000359033.4

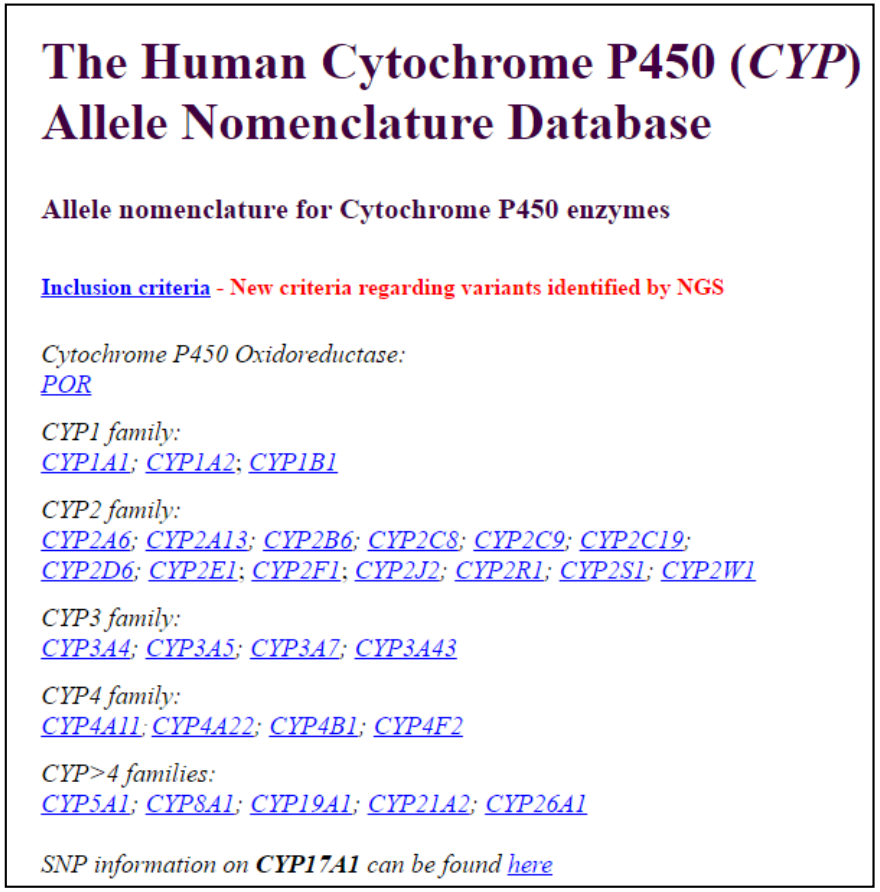
Ensembl Website

- Minor Allele Frequency: Population genetics
- Associated Studies
- Clinical Evidence
- Gene Function
- Sequence
- Linkage disequilibrium



CYP450 Allele Nomenclature Database

- Identification of the CYP450 Variants
- Nucleotide and Amino Acid Changes
- Consequences of the Variant
- References



The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database

Allele nomenclature for Cytochrome P450 enzymes

Inclusion criteria - New criteria regarding variants identified by NGS

Cytochrome P450 Oxidoreductase:
POR

CYP1 family:
CYP1A1; CYP1A2; CYP1B1

CYP2 family:
CYP2A6; CYP2A13; CYP2B6; CYP2C8; CYP2C9; CYP2C19; CYP2D6; CYP2E1; CYP2F1; CYP2J2; CYP2R1; CYP2S1; CYP2W1

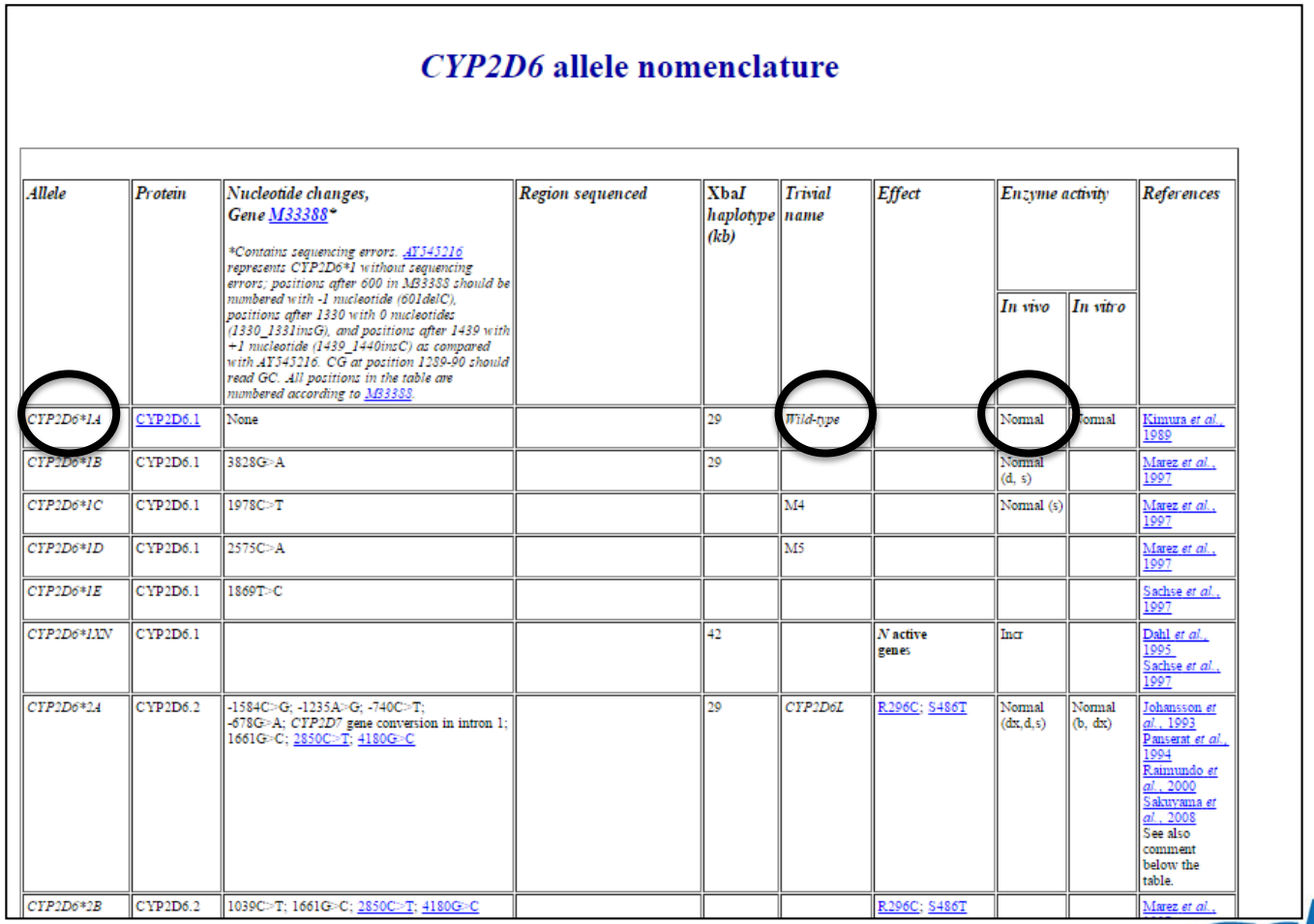
CYP3 family:
CYP3A4; CYP3A5; CYP3A7; CYP3A43

CYP4 family:
CYP4A11; CYP4A22; CYP4B1; CYP4F2

CYP>4 families:
CYP5A1; CYP8A1; CYP19A1; CYP21A2; CYP26A1

*SNP information on **CYP17A1** can be found here*

CYP450 Allele Nomenclature Database



CYP2D6 allele nomenclature

Allele	*Protein*	*Nucleotide changes, Gene M33388** **Contains sequencing errors. AY545216 represents CYP2D6*1 without sequencing errors; positions after 600 in M33388 should be numbered with -1 nucleotide (601delC), positions after 1330 with 0 nucleotides (1330_1331insG), and positions after 1439 with +1 nucleotide (1439_1440insC) as compared with AY545216. CG at position 1289-90 should read GC. All positions in the table are numbered according to M33388.*	*Region sequenced*	*XbaI haplotype (kb)*	*Trivial name*	*Effect*	*Enzyme activity*		*References*
							In vivo	*In vitro*	
*CYP2D6*1A*	CYP2D6.1	None		29	*Wild-type*		Normal	Normal	Kimura *et al.*, 1989
*CYP2D6*1B*	CYP2D6.1	3828G>A		29			Normal (d, s)		Marez *et al.*, 1997
*CYP2D6*1C*	CYP2D6.1	1978C>T			M4		Normal (s)		Marez *et al.*, 1997
*CYP2D6*1D*	CYP2D6.1	2575C>A			M5				Marez *et al.*, 1997
*CYP2D6*1E*	CYP2D6.1	1869T>C							Sachse *et al.*, 1997
*CYP2D6*1XN*	CYP2D6.1			42		*N* active genes	Incr		Dahl *et al.*, 1995 Sachse *et al.*, 1997
*CYP2D6*2A*	CYP2D6.2	-1584C>G; -1235A>G; -740C>T; -678G>A; *CYP2D7* gene conversion in intron 1; 1661G>C; 2850C>T; 4180G>C		29	*CYP2D6L*	R296C; S486T	Normal (dx,d,s)	Normal (b, dx)	Johansson *et al.*, 1993 Panserat *et al.*, 1994 Raimundo *et al.*, 2000 Sakuyama *et al.*, 2008 See also comment below the table.
*CYP2D6*2B*	CYP2D6.2	1039C>T; 1661G>C; 2850C>T; 4180G>C				R296C; S486T			Marez *et al.*,

Gene Databases

- NAT1 & NAT2 - http://nat.mbg.duth.gr
- UGT –UDP Glucuronosyltransferase genes – http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles
- ABC Transporters - http://htd.cbi.pku.edu.cn/ & http://nutrigene.4t.com/humanabc.htm/

Table of Pharmacogenomic Biomarkers in Drug Labeling

- http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
- Drug labeling may contain information on:
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Genotype-specific dosing
  - Mechanisms of drug action
  - Polymorphic drug target and disposition genes
- Over 160 Drug-Gene Pairs

Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup‡	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alectinib	Oncology	ALK	ALK gene rearrangement positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alirocumab	Endocrinology	LDLR	LDL receptor mutation heterozygotes	Indications and Usage, Adverse Reactions, Clinical Studies
Amitriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Anastrozole	Oncology	ESR1, PGR	Hormone receptor positive	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies
Arformoterol (1)	Pulmonary	UGT1A1	UGT1A1 poor metabolizers	Clinical Pharmacology
Arformoterol (2)	Pulmonary	CYP2D6	CYP2D6 intermediate or poor metabolizers	Clinical Pharmacology
Aripiprazole	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Use in Specific Populations, Drug Interactions, Clinical Pharmacology

The Pharmacogenomics Knowledgebase (PharmGKB)

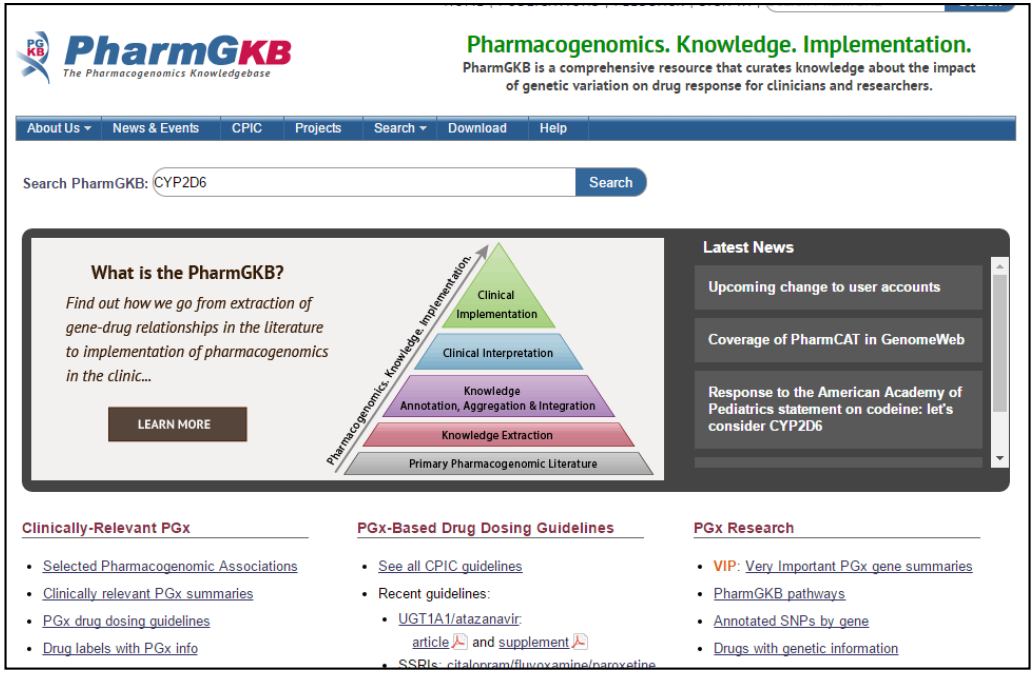
- Was developed by Stanford University with funding from the National Institutes of Health (NIH) and is a partner of the NIH Pharmacogenomics Research Network (PGRN).

- Began in 2000 with limited information on genomics and drug information - **www.pharmgkb.org**.

- Is currently a pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships.

The Pharmacogenomics Knowledgebase (PharmGKB)

- Includes dosing guidelines from several organizations:
  - Clinical Pharmacogenetics Implementation Consortium (CPIC) – 33 Drugs
  - Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG) – 54 Drugs
  - Canadian Pharmacogenomics Network for Drug Safety (CPNDS) – 5 Drugs



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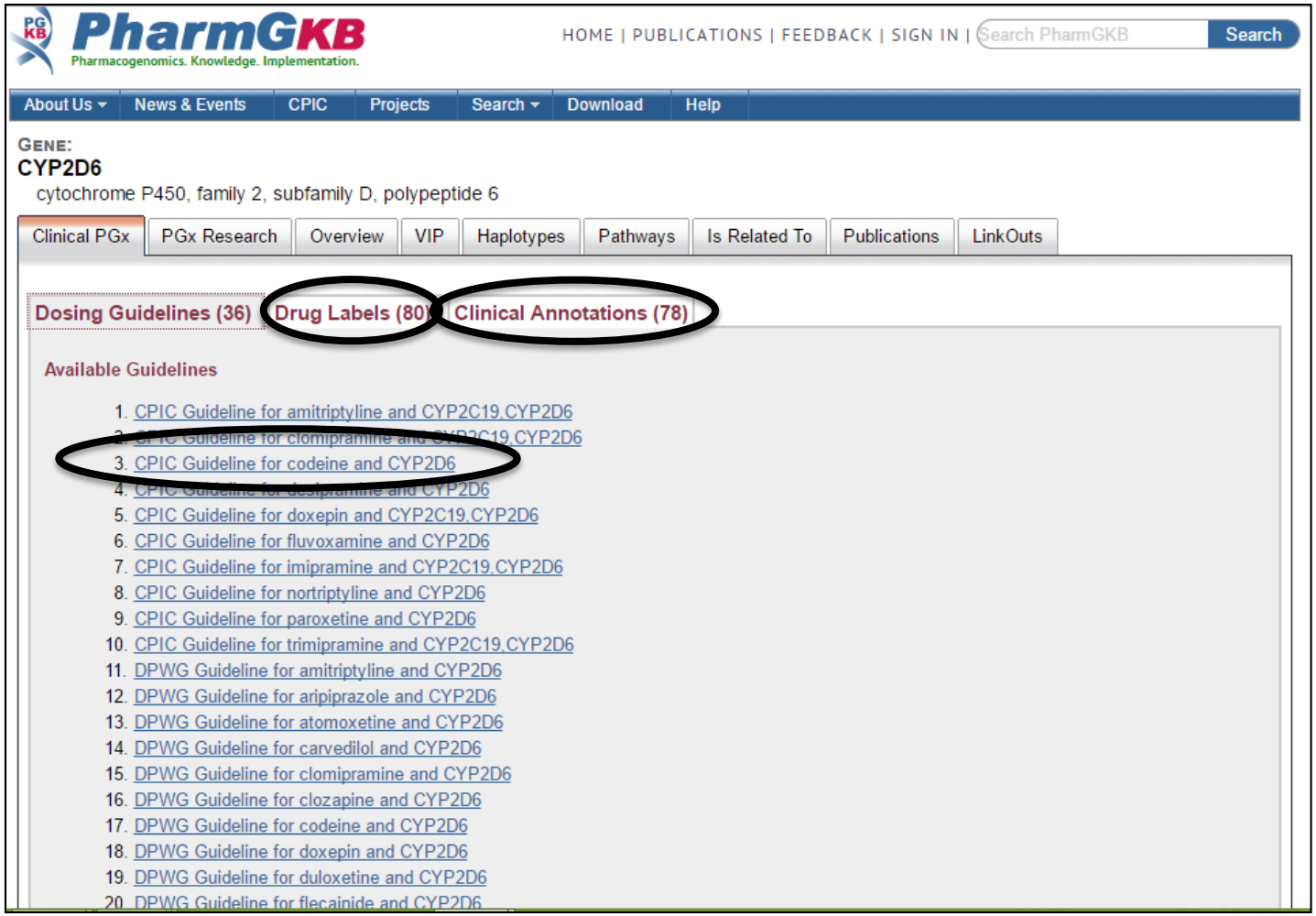
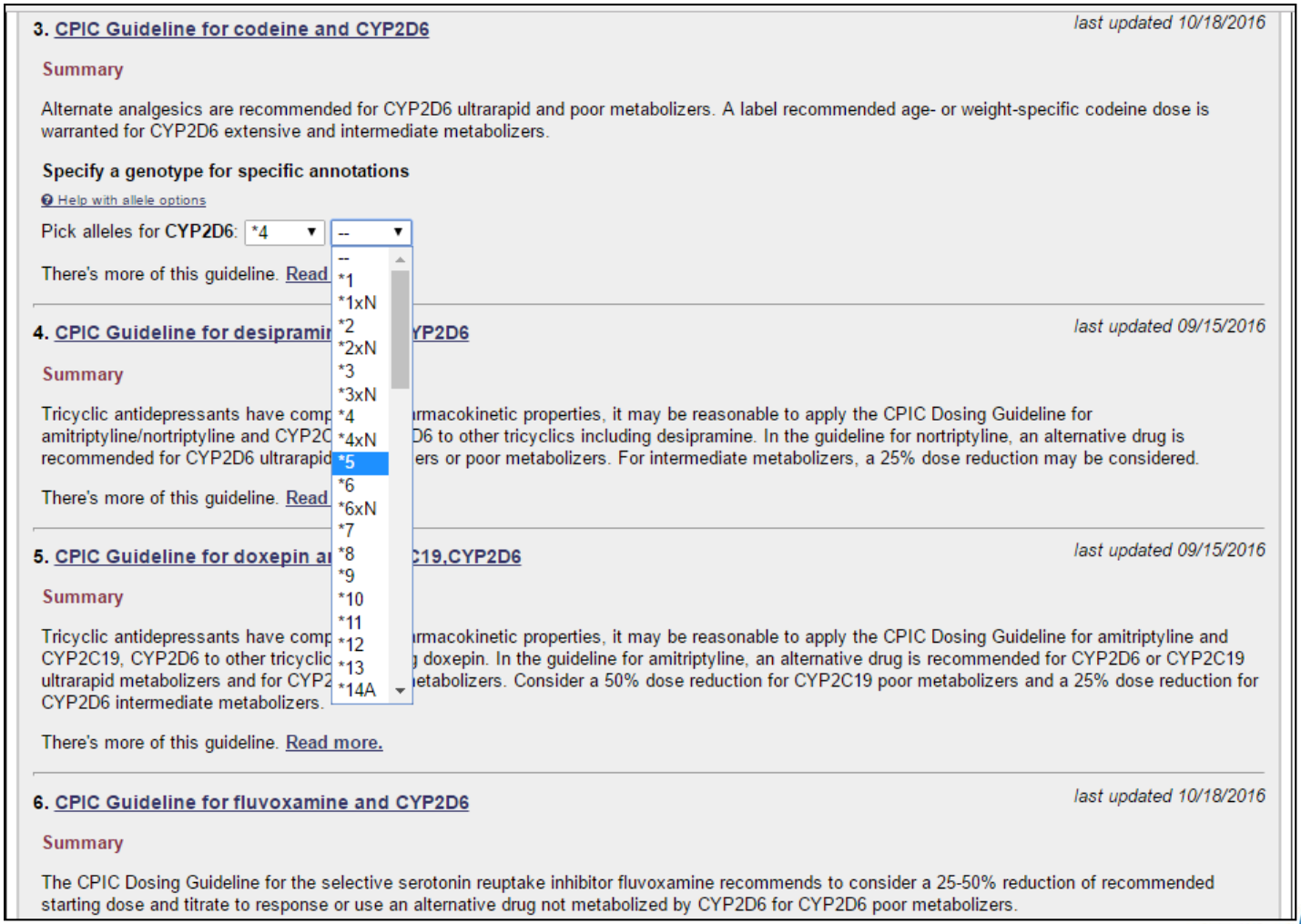
PharmGKB



PharmGKB



3. CPIC Guideline for codeine and CYP2D6 — *last updated 10/18/2016*

Summary

Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended age- or weight-specific codeine dose is warranted for CYP2D6 extensive and intermediate metabolizers.

Specify a genotype for specific annotations

Help with allele options

Pick alleles for **CYP2D6**: *4 --

There's more of this guideline. Read

--
*1
*1xN
*2
*2xN
*3
*3xN
*4
*4xN
*5
*6
*6xN
*7
*8
*9
*10
*11
*12
*13
*14A

4. CPIC Guideline for desipramin YP2D6 — *last updated 09/15/2016*

Summary

Tricyclic antidepressants have comp rmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline/nortriptyline and CYP2C D6 to other tricyclics including desipramine. In the guideline for nortriptyline, an alternative drug is recommended for CYP2D6 ultrarapid ers or poor metabolizers. For intermediate metabolizers, a 25% dose reduction may be considered.

There's more of this guideline. Read

5. CPIC Guideline for doxepin a C19,CYP2D6 — *last updated 09/15/2016*

Summary

Tricyclic antidepressants have comp rmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclic doxepin. In the guideline for amitriptyline, an alternative drug is recommended for CYP2D6 or CYP2C19 ultrarapid metabolizers and for CYP2 etabolizers. Consider a 50% dose reduction for CYP2C19 poor metabolizers and a 25% dose reduction for CYP2D6 intermediate metabolizers.

There's more of this guideline. Read more.

6. CPIC Guideline for fluvoxamine and CYP2D6 — *last updated 10/18/2016*

Summary

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor fluvoxamine recommends to consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6 for CYP2D6 poor metabolizers.

PharmGKB

3. CPIC Guideline for codeine and CYP2D6 *last updated 10/18/2016*

Summary

Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended age- or weight-specific codeine dose is warranted for CYP2D6 extensive and intermediate metabolizers.

Specify a genotype for specific annotations

Help with allele options

Pick alleles for **CYP2D6**: *4 ▾ *5 ▾

Activity Score	0
Implications	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief
Metabolizer Status	Poor metabolizer
Phenotype (Genotype)	An individual carrying no functional alleles
Recommendations	Avoid codeine use due to lack of efficacy. Considerations for alternative opioids: Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided. There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol post-surgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable. Some other opioid analgesics are metabolized by CYP2D6, such as hydrocodone and oxycodone. 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 ultrarapid metabolizers.
Classification of Recommendation	Strong

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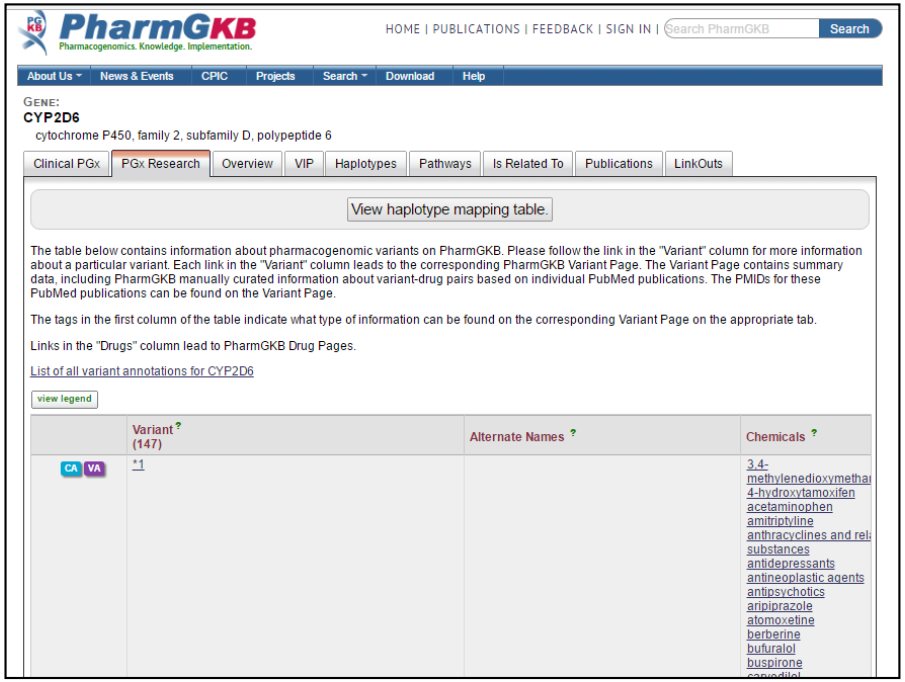
- Guidelines are a reflection of a clinical consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research.

- Register will help to gain access to the research information.



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GENE:
CYP2D6
cytochrome P450, family 2, subfamily D, polypeptide 6

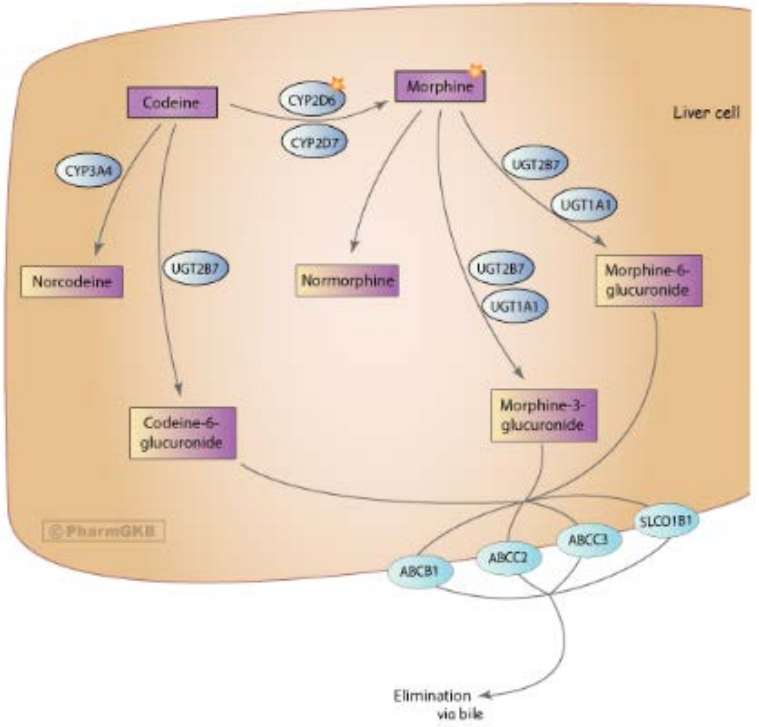
Clinical PGx | PGx Research | Overview | VIP | Haplotypes | Pathways | Is Related To | Publications | LinkOuts

PharmGKB Curated Pathways

Pathways created internally by PharmGKB based primarily on literature evidence.

1. Acetaminophen Pathway (therapeutic doses), Pharmacokinetics
   Stylized diagram showing acetaminophen metabolism and transport in the liver.
2. Acetaminophen Pathway (toxic doses), Pharmacokinetics
   Stylized diagram showing acetaminophen metabolism at higher acetaminophen doses (toxic doses) in the liver
3. Atorvastatin/Lovastatin/Simvastatin Pathway, Pharmacokinetics
   Drug-specific representation of the candidate genes involved in transport, metabolism and clearance.
4. Benzodiazepine Pathway, Pharmacokinetics
5. Celecoxib Pathway, Pharmacokinetics
6. Citalopram Pathway, Pharmacokinetics
   Pharmacokinetics of the selective serotonin reuptake inhibitor citalopram.
7. Clomipramine Pathway, Pharmacokinetics
   Schematic representation of clomipramine metabolism in human liver.
8. Codeine and Morphine Pathway, Pharmacokinetics
   Representation of the candidate genes involved in metabolism of codeine and morphine
9. Doxepin Pathway, Pharmacokinetics
   Stylized liver cell showing candidate genes involved in the metabolism of the tricyclic doxepin

Representation of the candidate genes involved in metabolism of codeine and morphine.



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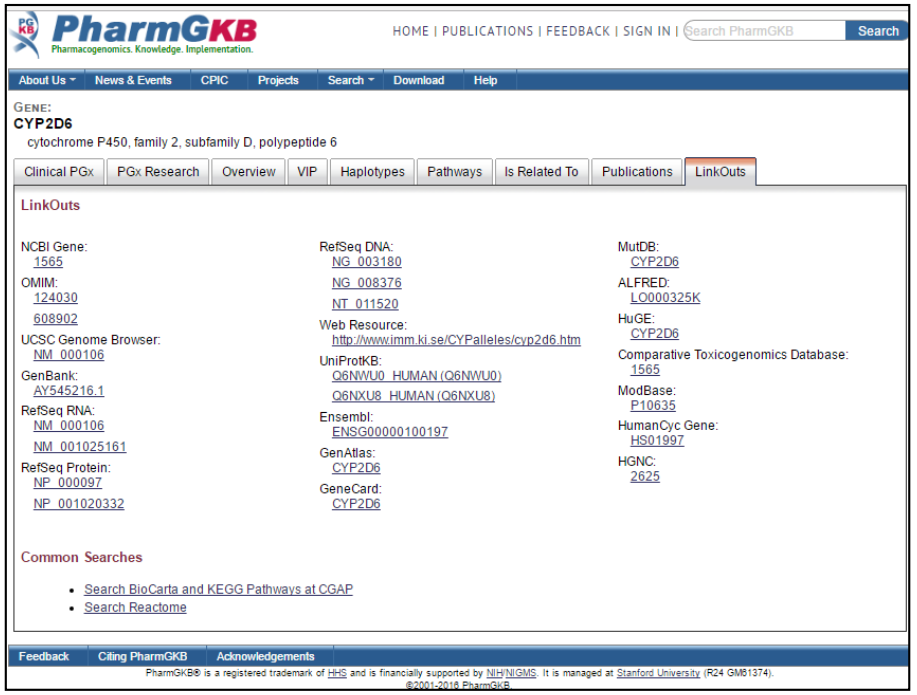
Online Resources

- References
- Other databases/gene browsers
  - NCBI
  - Ensembl
  - Online Mendelian Inheritance in Man (OMIM)
  - GeneCard



Specialized Pharmacogenomic & Other Related Websites

- Warfarin Dosing based on genotype of CYP2C9 & VKORC1:

http://www.warfarindosing.org/Source/Home.aspx

- Antiviral treatment for HIV based on viral genome mutations: https://hivdb.stanford.edu/

- Cancer gene related markers (targets/resistance): https://www.mycancergenome.org/ http://www.cancerrxgene.org/translation/Drug

Pharmacogenomic Websites

- Clinical Decision Support KnowledgeBase (cdskb) - https://cdskb.org/
- Clinical Genome Resource (ClinGen) - https://www.clinicalgenome.org/
- Clinical Pharmacogenetics Implementation Consortium (CPIC) - https://cpicpgx.org/
- Community Pharmacist Pharmacogenetics Network (CPPN) - http://rxpgx.com/
- EGenetics/Genomics Competency Center (G2C2) - http://g-2-c-2.org//
- Implementing Genomics in Practice (IGNITE) - https://ignite-genomics.org/
- National Human Genome Research Institute - https://www.genome.gov/

Be Careful of Online Resources

- SNPedia – is a wiki investigating human genetics.
  - There are currently 87842 SNPs in SNPedia.
  - Tested through companies such as 23andMe, Ancestry, deCODEme, FamilyTreeDNA
  - Same resources as other sites – dbSNP, PharmGKB, ensembl, and gwascentral.

- DrugBank – is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information.

Multiple Choice Question

Which of the following resources is the best for clinical information about pharmacogenomics?

A. www.ensembl.org
B. www.ncbi.gov
C. www.pharmgkb.org
D. www.snpedia.com

Points About Pharmacogenomics

- Importance of pharmacogenomics:
  - Maximize the benefits.
  - Decrease the potential for adverse drug reactions.
- Several genetic resources are available
  - Best gene browsers – NCBI & Ensembl
  - PharmaGKB is able to give clinical guidelines for some medications

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270-L01- Fitting into Our Genes: Demystifying Pharmacogenomic Tests Using Online Databases

Part 2

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Disclosures

- Financial disclosure not related to the topic of discussion:
  - BioQ Pharma
    - BioQ Pharma is a specialty pharmaceutical company focused on infusible drugs
- Non-financial disclosure:
  - Author in: Concepts in Pharmacogenomics
    - Publisher: ASHP Publications 2016

Objectives

- At the end of this presentation, the audience should be able to:
  - Discuss the role of ABC transporters in drug resistance, metabolism, and toxicity
  - Determine the appropriate online resources for pharmacists and clinicians to understand PGx test results
  - Explain the significance of ABC transporter-drug interactions as required by the FDA on package inserts
  - Design a medication regimen based on pharmacogenomic test results

I have seen new package inserts with ABC transporter information included

A. True

B. False

C. What is a “package insert”?

Case

- EG is a 34 year old Caucasian male with a history of hyperlipidemia and GERD. He is being discharged from the hospital today on tedizolid for a MRSA infection. EG has been on rosuvastatin 10mg PO daily for hyperlipidemia and plans to continue the rosuvastatin upon discharge.
- You are alerted regarding the following drug-drug interaction while verifying the order for tedizolid:

Case Continued

7 DRUG INTERACTIONS

Orally administered SIVEXTRO inhibits Breast Cancer Resistance Protein (BCRP) in the intestine, which can increase the plasma concentrations of orally administered BCRP substrates, and the potential for adverse reactions. If possible, an interruption in the treatment of the co-administered BCRP substrate medicinal product should be considered during treatment with SIVEXTRO, especially for BCRP substrates with a narrow therapeutic index (e.g., methotrexate or topotecan). If coadministration cannot be avoided, monitor for adverse reactions related to the concomitantly administered BCRP substrates, including rosuvastatin. [*See Clinical Pharmacology (12.3).*]

SIVEXTRO (Tedizolid Phosphate) Package Insert. Accessed October 5th, 2016 at: http://www.merck.com/product/usa/pi_circulars/s/sivextro/sivextro_pi.pdf

Based on the known information, which one of the following is the most appropriate course of action?

A. Increase rosuvastatin dose

B. Decrease rosuvastatin dose by ~50%

C. Continue current rosuvastatin dose

D. None of the above

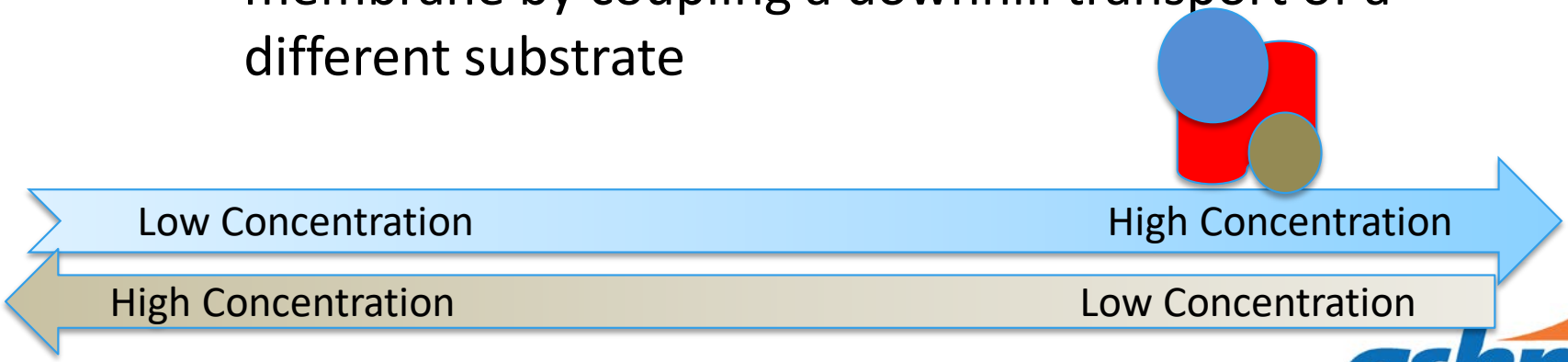
Transporters

- More than 400 transporters encoded in the human genome
- Two major transporter super families within humans
  - Solute Carrier (SLC) transporters
    - > 300 influx transporters for nutrient and drug cell/organ uptake
  - ATP-Binding Cassette (ABC) transporters
    - 49 members with 7 subfamilies

Liang Y. Protein Cell 2015;6(5)334-350
Li Y. Adv Drug Delivery Rev 2016. Ahead of Print ADR 13061

SLC Transporters

- SLC transporters:
  - Facilitative transporters
    - Transport substrates down the gradient across a membrane
  - Active transporters
    - Transport substrates against a gradient across the membrane by coupling a downhill transport of a different substrate



Liang Y. Protein Cell 2015;6(5)334-350

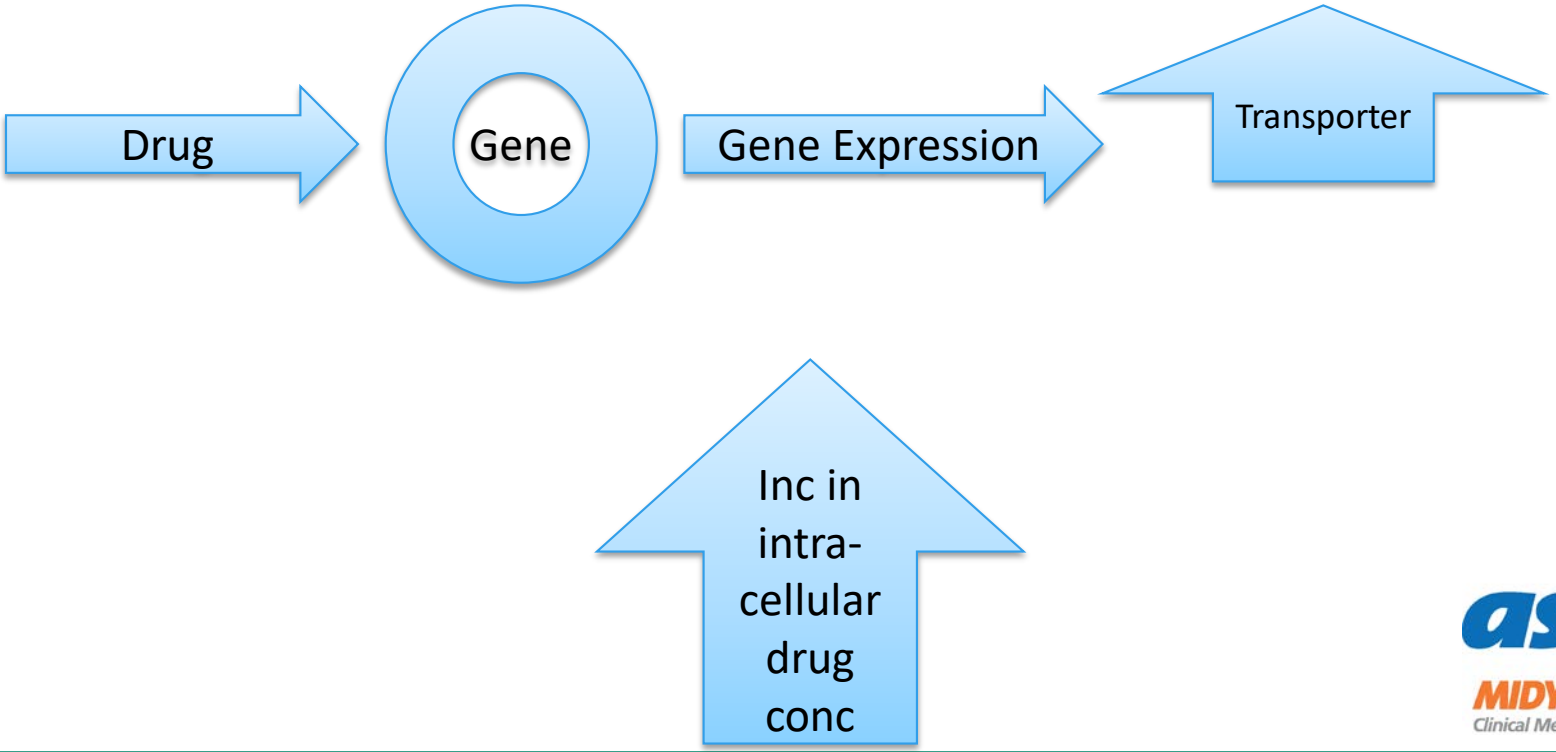
SLC Transporters

Gene	Protein	Location	Substrates
SLC22A1	OCT1	Liver	Thiamine, acetylcholine, metformin, acyclovir, lamivudine, pentamidine, palitacel, and oxaliplatin
SLC22A2	OCT2	Kidney	Creatinine, bile acids, acetylcholine, norepinephrine, serotonin, metformin, pindolol, propranolol, ranitidine, cisplatin, famotidine, lamivudine, and procanimide
SLA22A3	OCT3	Kidney, liver, placenta, heart, and skeletal muscle	Creatinine, acetylcholine, dopamine, norepinephrine, serotonin, histamine, progesterone, testosterone, lidocaine, atropine, prazosin, metformin, ranitidine, verapamil, mitoxantrone, and lamivudine
SLC22A 4-5	OCTN	Ubiquitously expressed	Acetylcholine, pregabalin, tiotropium, doxorubicin, etoposide, verapamil
SLC22A6	OAT	Kidney>liver and brain	Adefovir, zidovudine, cipro, methotrexate, pravastatin, antibiotics, NSAIDS, diuretics

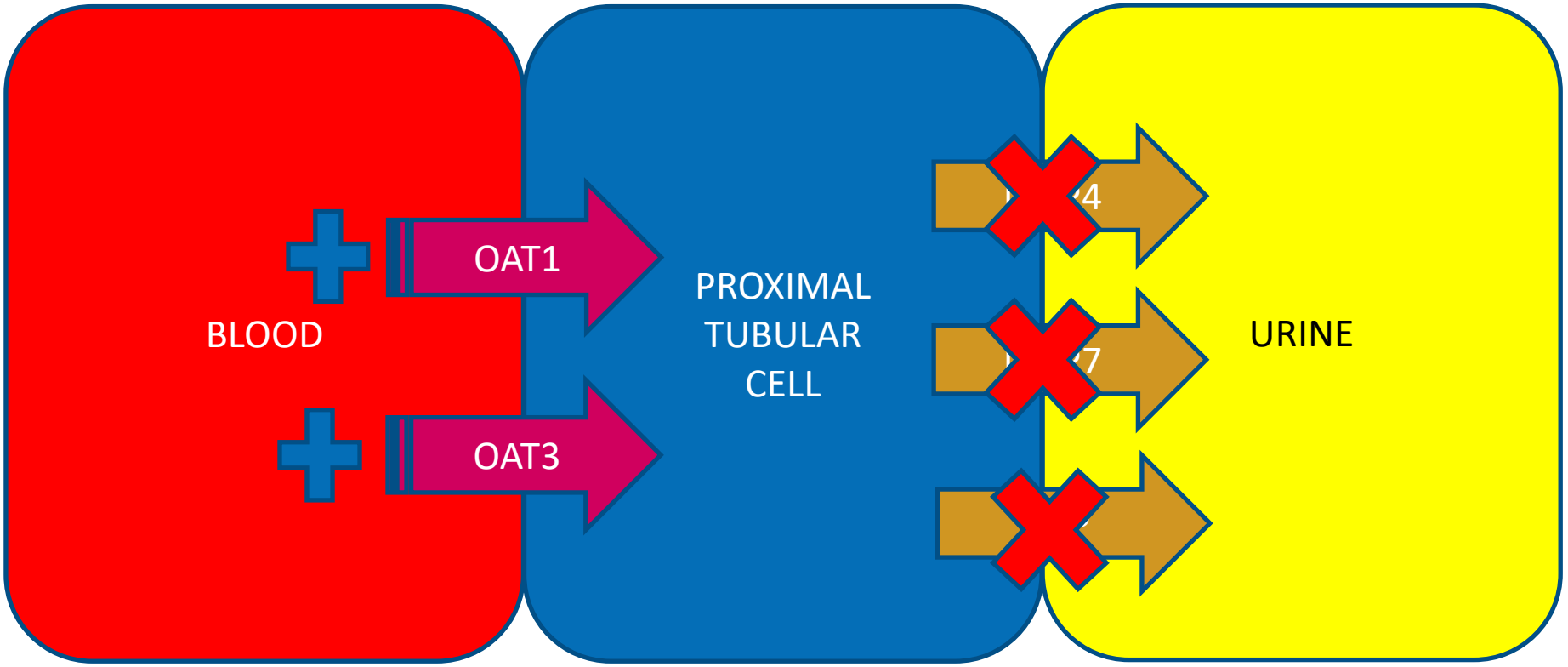
Liang Y. Protein Cell 2015;6(5)334-350

SLC Transporters

- Various SLC transporters (especially OAT) are associated with drug toxicity due to upregulation of the transporters
  - Associated with **renal**, liver, and heart disease



SLC Transporters

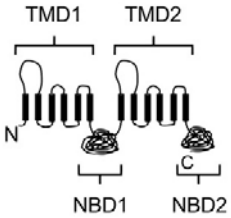
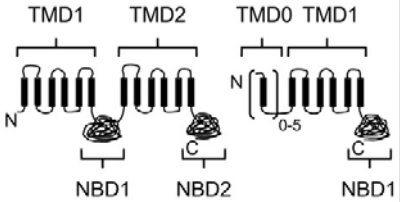
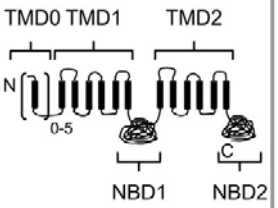
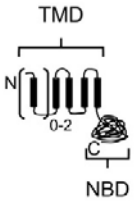
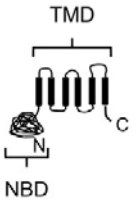


Adapted from Pharmacogen J 2015:1-5

ABC Transporters

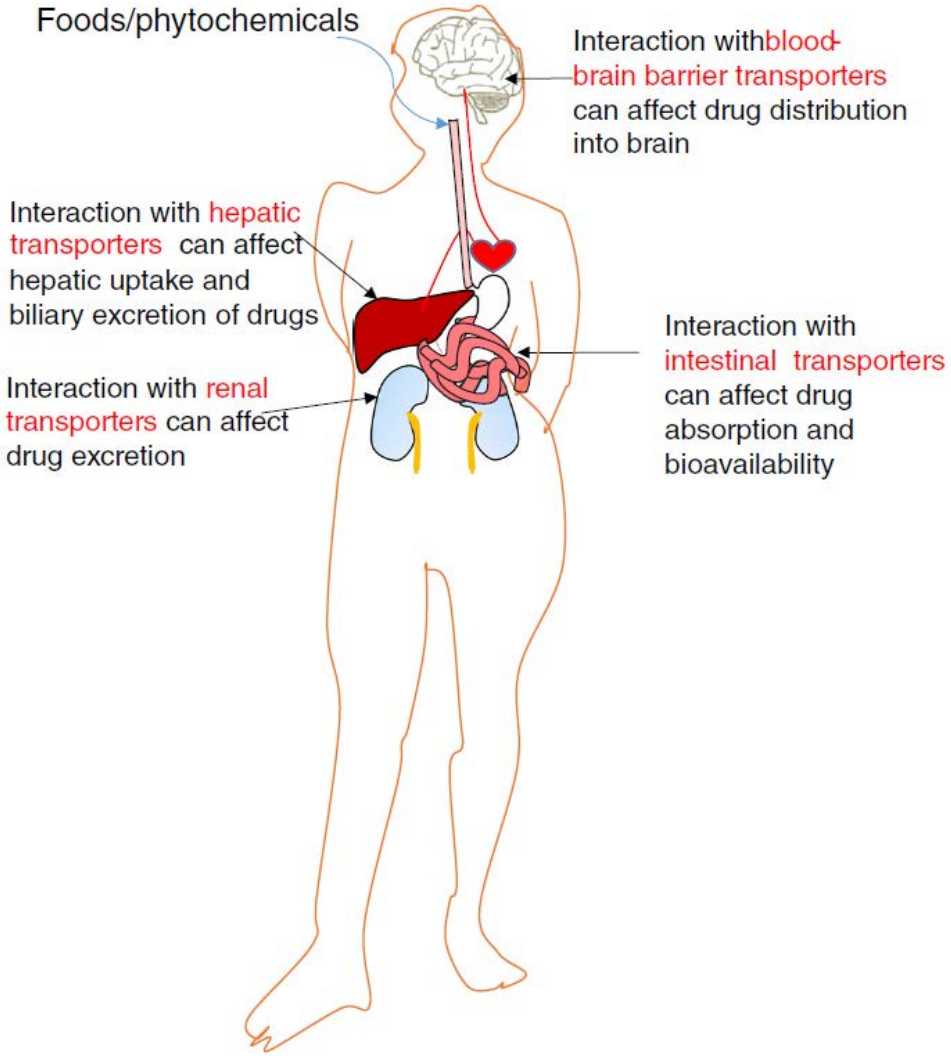
- Present in humans, animals, plants, and bacteria
- Considered efflux pumps (vs influx as with SLC transporters)
- Consist of families from ABCB-G
  - E and F are not membrane transporters
- In addition they play a role in:
  - Potassium channels (SUR1, SUR2)
  - Chloride channels (CFTR)
  - Immunity (ABCB2, ABCB3)
  - Bile breakdown (ABCB11, ABCB4, ABCG5, ABCG8)

Li W. Drug Resist update 2016;27:14-19
Locher K. Nat Struct Molec Bio 2016;23(6): 487-493
Theodoulou F. Biochem Soc. Trans 2015;43:1033-1039

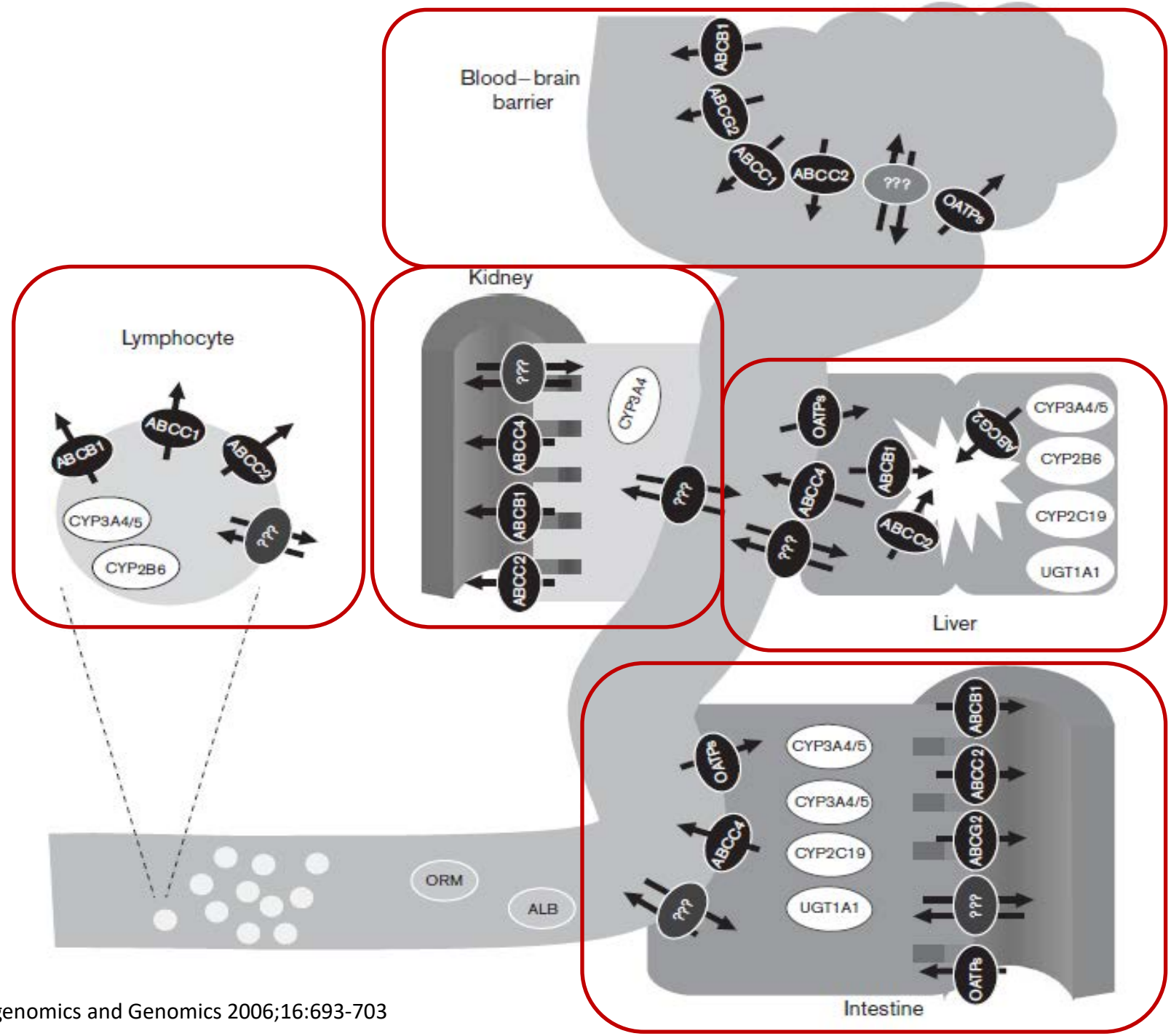
Human ABC-Family	A	B	C	D	G
Transporter Topology					
Lipophilic Substrates	(Phospho)lipids (A1, A3, A4, A7, A12) Sphingomyelin (A1, A3) Cholesterol (A1, A2, A5)	Phospholipids (B1, B4) Sphingolipids (B1) Bile salts (B11) Drugs (B1)	Phospholipids (C1) Bile salts (C1, C2, C3) Steroids (C1, C10) Drugs (C1, C2)	(VLC)FA (D1-D4)	Lipids (G4) Cholesterol (G1, G4, G5/G8) Steroids (G2, G5/G8) Drugs (G2)
Subcellular Localization	Plasma membrane (A1, A4, A7) Lysosome (A2, A5) Lamellar bodies (A3, A12)	Plasma membrane (B1, B4, B11)	Plasma membrane (C1, C2, C3, C10)	Peroxisome (D1-D4)	Plasma membrane (G5/G8) Endosomes (G1, G4)

Neumann J. Biochimica et Biophysica Acta 2016. Ahead of Print

ABC Transporter Locations

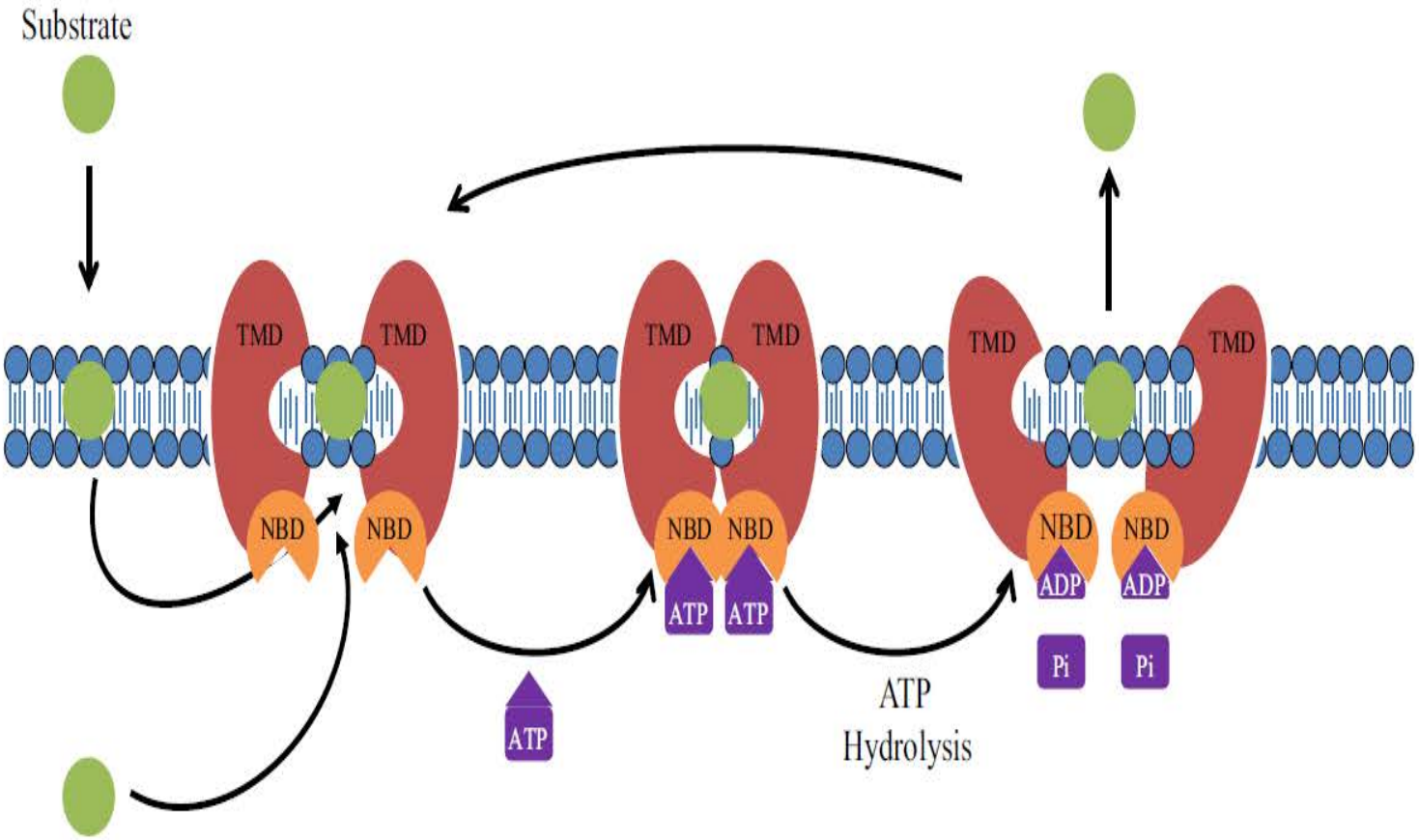


Li Y. Adv Drug Delivery Rev 2016. Ahead of Print ADR 13061



Pharmacogenomics and Genomics 2006;16:693-703

ABC Transporters



Chen Z. Cancer Letters 2016;370:153-164

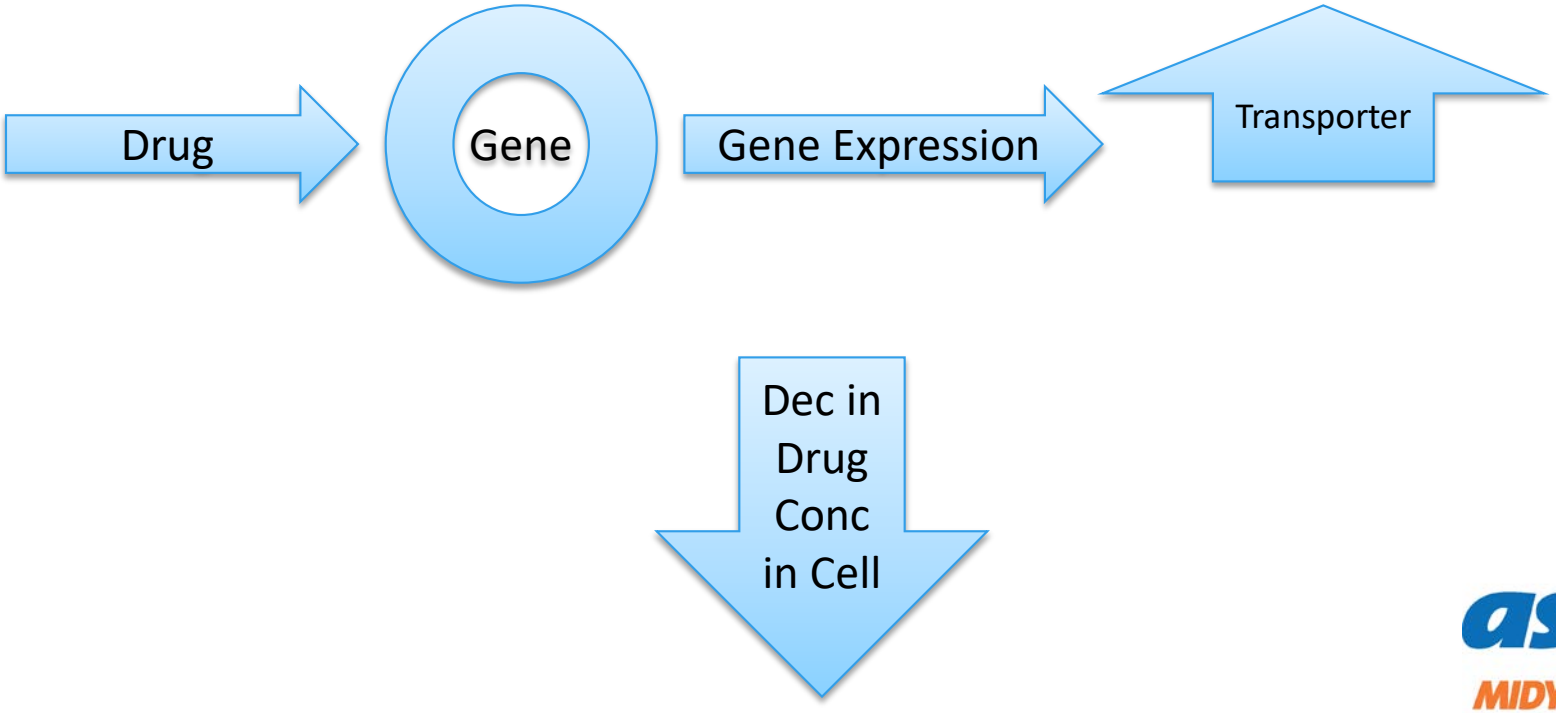
ABC Transporters

- ABC genes are able to affect:
  - ABC transporter location (intracellular vs extracellular)
  - Tumor cell proliferation and invasion
  - Defense against antitumor regulatory pathways
    - Decreased apoptosis and complement mediated cytotoxicity

Locher K. Nat Struct Molec Bio 2016;23(6): 487-493

ABC Transporters - Resistance

- Various ABC transporters are associated with drug resistance due to increased ABC transporter gene expression



ABC Transporters

- Medications can act as:
  - Inhibitor of ABC
    - Inhibition of gene expression
    - Inhibition of transporter
  - Inducer of ABC
    - Inducer of gene expression
  - Substrate for ABC transporter

ABC Transporters

- The most significant ABC transporters are

  Gene/Transporter

  - *ABCB1*/ABCB1 (P-glycoprotein)
  - *ABCG2*/BCRP

ABC Transporters – ABCB1

- ABCB1 (Pgp) is the most studied ABC transporter
  - Discovered in 1976
  - First discovered in colchicine resistant cells
  - Location:
    - Kidney proximal tubule epithelia
    - Liver
    - Placenta
    - BBB
    - GI tract (Colon > large intestines > small intestines > stomach)

Chen Z. Cancer Letters 2016;370:153-164

ABC Transporters – ABCB1

Export of xenobiotics from cells into extracellular spaces (e.g. at the BBB) or out of the body (e.g. in the gut) and for renal and hepatic clearance

Colchicine resistance, uterine sarcoma, soft tissue sarcoma, breast cancer, inflammatory bowel disease 13, lung cancer, acute myeloid leukemia, myeloma, warfarin sensitivity, postural hypotension, cannabis dependence, vaginitis, plasmablastic lymphoma, pervasive developmental disorder, microsporidiosis, ileus, neonatal abstinence syndrome, 5-fluorouracil toxicity, paralytic ileus, engraftment syndrome, ovarian cystadenocarcinoma, acute non lymphoblastic leukemia

Digoxin, loperamide, berberine, irinotecan, doxorubicin, vinblastine, paclitaxel, fexofenadine, seliciclib

ABC Transporters – ABCG2

- ABCG2 was first discovered in breast cancer cells resulting in resistance to mitoxantrone
- Half-transporter (homodimer)
- Location:
  - Intestine, liver, brain (including BBB), plasma membranes, apical surface of proximal tubule cells, hepatocytes
- Implicated in causing gout and decreased uric acid excretion

Chen Z. Cancer Letters 2016;370:153-164
Theodoulou F. Biochem Soc. Trans 2015;43:1033-1039

ABC Transporters – ABCG2

Regulation of intestinal absorption, biliary and renal secretion of substrates and protection of the fetus and brain from toxins; a major role in the multidrug resistance	Breast cancer, choriocarcinoma, erythroplakia, acute lymphocytic leukemia, dysembryoplastic neuroepithelial tumor, adult acute lymphocytic leukemia, nonpapillary renal cell carcinoma, acute myeloid leukemia	Anthracyclines, daunorubicin, doxorubicin, topotecan, SN-38, irinotecan, methotrexate, imatinib, irinotecan, mitoxantrone, nucleoside analogs, prazosin, pantoprazole, statins, topotecan

Selected substrates of P-gp/ABCB1, MRP2/ABCC2 and BCRP/ABCG2.

P-gp/ABCB1	**Analgesics**: asimadoline, fentanyl, morphine, pentazocine **Antiarrhythmics**: amiodarone, digoxin, lidocaine, propafenone, quinidine, verapamil **Antibiotics**: cefoperazone, ceftriaxone, clarithromycin, doxycycline, erythromycin, gramicidin A, gramicidin D, grepafloxacin, itraconazole, ketoconazole, levofloxacin, rifampicin, sparfloxacin, tetracycline, valinomycin **Anticancer drugs**: 5-fluorouracil, actinomycin D, bisantrene, chlorambucil, colchicine, cisplatin, cytarabine, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, gefitinib, hydroxyurea, irinotecan (CPT-11), methotrexate, mitomycin C, mitoxantrone, paclitaxel, tamoxifen, teniposide, topotecan, vinblastine, vincristine **Antihistamines**: cimetidine, fexofenadine, ranitidine, terfenadine **Antilipidemic**: lovastatin, simvastatin **Calcium channel blockers**: azidopine, bepridil, diltiazem, felodipine, nifedipine, nisoldipine, nitrendipine, tiapamil, verapamil **Fluorescent dyes**: calcein AM (calcein acetoxymethylester), Hoechst 33342, rhodamine 123 **HIV-protease inhibitors**: amprenavir, indinavir, lopinavir, nelfinavir, saquinavir, ritonavir **Immunosuppressive agents**: cyclosporin A, cyclosporin H, FK506, sirolimus, tacrolimus, valspodar (PSC-833) **Natural products**: curcuminoids, flavonoids **Neuroleptics**: chlorpromazine, phenothiazine **Others**: BCECF-AM, bepridil, calcein-AM, diltiazem, endosulfan, leupeptin, methyl parathion, paraquat, pepstatin A, trifluoperazine, trans-flupentixol
MRP2/ABCC2	**Antibiotics:** ampicillin, azithromycin, cefodizime, ceftriaxone, grepafloxacine, irinotecan **Anticancer drugs**: cisplatin, doxorubicin, epirubicin, etoposide, irinotecan, mitoxantrone, methotrexate, SN-38, vinblastine, vincristine **Antihypertensives:** olmesartan, temocaprilate **HIV drugs**: adevovir, cidofovir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir **Others:** ethinylestradiol-3-O-glucuronide, genistein-7-glucoside, p-Aminohippurate, phloridzin, quercetin 4′-β-glucoside, *vinca* alkaloids
BCRP/ABCG2	**Antibiotics**: ciprofloxacin, norfloxacin, ofloxacin **Anticancer drugs**: daunorubicin, doxorubicin, epirubicin, etoposide, gefitinib, imatinib, irinotecan, mitoxantrone, methotrexate, SN-38, teniposide, topotecan, **Antivirals**: delavirdine, lopinavir, lamivudine, nelfinavir, zidovudine **Antihypertensives**: reserpine **Calcium channel blockers:** nicardipine **Lipid lowering drugs:** cerivastatin, pravastatin, rosuvastatin **Others**: azidothymidine, chrysin, cyclosporin A, lamivudine, ortataxel, quercetin

Chen Z. Cancer Letters 2016;370:153-164

ABC Transporters and Diseases

ABC transporter	Disease
ABCA1	Tangier disease and familial high density lipoprotein (HDL) deficiency; atherosclerosis; Alzheimer's disease
ABCA3	Neonatal surfactant deficiency and pulmonary fibrosis; congenital cataract
ABCA4	Stargardt macular degeneration
ABCA7	Alzheimer's disease
ABCA12	Harlequin and lamellar ichthyosis
ABCB1/transporter associated with antigen processing (Tap)2; ABCB2/Tap1	Immune deficiency; arthritis risk
ABCB4/MDR2	PFIC3; other types of cholestasis
ABCB7	Sideroblastic amaemia and ataxia
ABCB11/bile salt export pump (BSEP)	PFIC2; intrahepatic cholestasis of pregnancy; neonatal respiratory distress syndrome
ABCC2/MRP2	Dubin–Johnson syndrome
ABCC5/MRP5	Inherited hypertrichosis
ABCC6/MRP6	Pseudoxanthoma elasticum
ABCC7/CFTR	CF
ABCC8/SUR1	Diabetes
ABCC9/SUR2	Diabetes
ABCD1/adrenoleukodystrophy protein (ALDP)	X-linked adrenoleukodystrophy X-linked adrenomyeloneuropathy
ABCD3/peroxisome membrane protein (PMP70)	Hepatosplenomegaly; liver disease
ABCD4/PMP69	Inborn error of vitamin B12 metabolism
ABCG2/breast cancer resistance protein (BCRP)	Gout and hyperuricaemia
ABCG5; ABCG8	Sitosterolemia; coronary heart disease; gallstone disease
ABCB1/P-gp; ABCC1/MRP1, ABCG2/BCRP	Multi-drug resistance
ABCC2-6	Drug transport

Theodoulou F. Biochem Soc. Trans 2015;43:1033-1039

Case Continued

Membrane Transporters

The potential for tedizolid or tedizolid phosphate to inhibit transport of probe substrates of important drug uptake (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP) was tested *in vitro*. No clinically relevant interactions are expected to occur with these transporters except BCRP.

Coadministration of multiple oral doses of SIVEXTRO (200 mg once daily) increased the Cmax and AUC of rosuvastatin (10 mg single oral dose), a known BCRP substrate, by approximately 55% and 70%, respectively, in healthy subjects [*see Drug Interactions (7)*].

SIVEXTRO (Tedizolid Phosphate) Package Insert. Accessed October 5th, 2016 at: http://www.merck.com/product/usa/pi_circulars/s/sivextro/sivextro_pi.pdf

Based on the known information, which one of the following is the most appropriate course of action?

A. Increase rosuvastatin dose

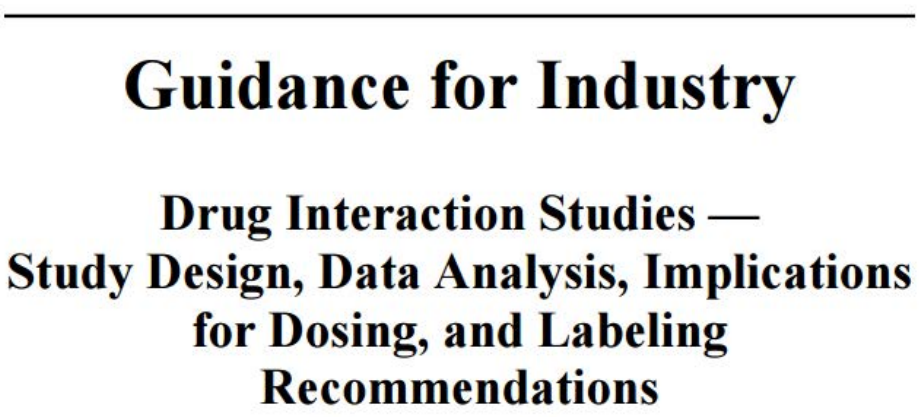
B. Decrease rosuvastatin dose by ~50%

C. Continue current rosuvastatin dose

D. None of the above

FDA and ABC Transporters

- 5 of 12 drug withdrawn from the U.S. between 1997-2002 exhibited metabolic drug-drug interactions
- The U.S. Food and Drug Administration (FDA) has issued a Guidance for Industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process – Studies in Vitro"
  - This guidance was first issued in 1997
  - Updated in 2006


Guidance for Industry

Drug Interaction Studies —
Study Design, Data Analysis, Implications
for Dosing, and Labeling
Recommendations

Drug Development and Drug Interactions

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

- CYP Enzymes
  - In vitro
    - In vitro marker reactions
    - In vitro selective inhibitors
    - In vitro inducers
  - Clinical index drugs
    - Clinical index substrates
    - Clinical index inhibitors
    - Clinical index inducers
  - Examples of clinical substrates, inhibitors, and inducers
    - Clinical substrates
    - Clinical inhibitors
    - Clinical inducers
- Transporters
  - In vitro
    - In vitro substrates
    - In vitro inhibitors
  - Examples of clinical substrates, inhibitors and inducers
    - Clinical substrates
    - Clinical inhibitors

Table 5-1: Examples of clinical substrates for transporters (for use in clinical DDI studies and/or drug labeling) (9/26/2016)

Transporter	Gene	Substrate
P-gp	*ABCB1*	dabigatran, digoxin, fexofenadine[e]
BCRP	*ABCG2*	rosuvastatin, sulfasalazine
OATP1B1 OATP1B3	*SLCO1B1*, *SLCO1B3*	asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel[a], fexofenadine[e], glyburide, nateglinide, paclitaxel, pitavastatin[b], pravastatin, repaglinide, rosuvastatin[b], simvastatin acid
OAT1 OAT3	*SLC22A6*, *SLC22A8*	adefovir[c], cefaclor, ceftizoxime, famotidine[d], furosemide, ganciclovir[c], methotrexate, oseltamivir carboxylate[d], penicillin G[d]
MATE1, MATE-2K, OCT2	*SLC47A1*, *SLC47A2*, *SLC22A2*	dofetilide, metformin

Note:
Criteria for selecting clinical substrates are as follows:

- P-gp: (1) AUC fold-increase≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.
- BCRP: (1) AUC fold-increase≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.
- OATP1B1/OATP1B3: (1) AUC fold-increase≥2 with rifampin (single dose) or cyclosporine A co-administration, or pharmacogenetic alteration of SLCO1B1 (521T>C) and (2) in vitro transport by OATP1B1 or OATP1B3 expression systems.
- OAT1/OAT3: (1) AUC fold-increase≥1.5 with probenecid co-administration, (2) fraction excreted unchanged into urine as an unchanged drug ≥ 0.5, and (3) in vitro transport by OAT1 or OAT3 expression systems.
- OCT2/MATE: Well-established substrate of cationic transport system (metformin) and a narrow therapeutic-index drug (dofetilide).

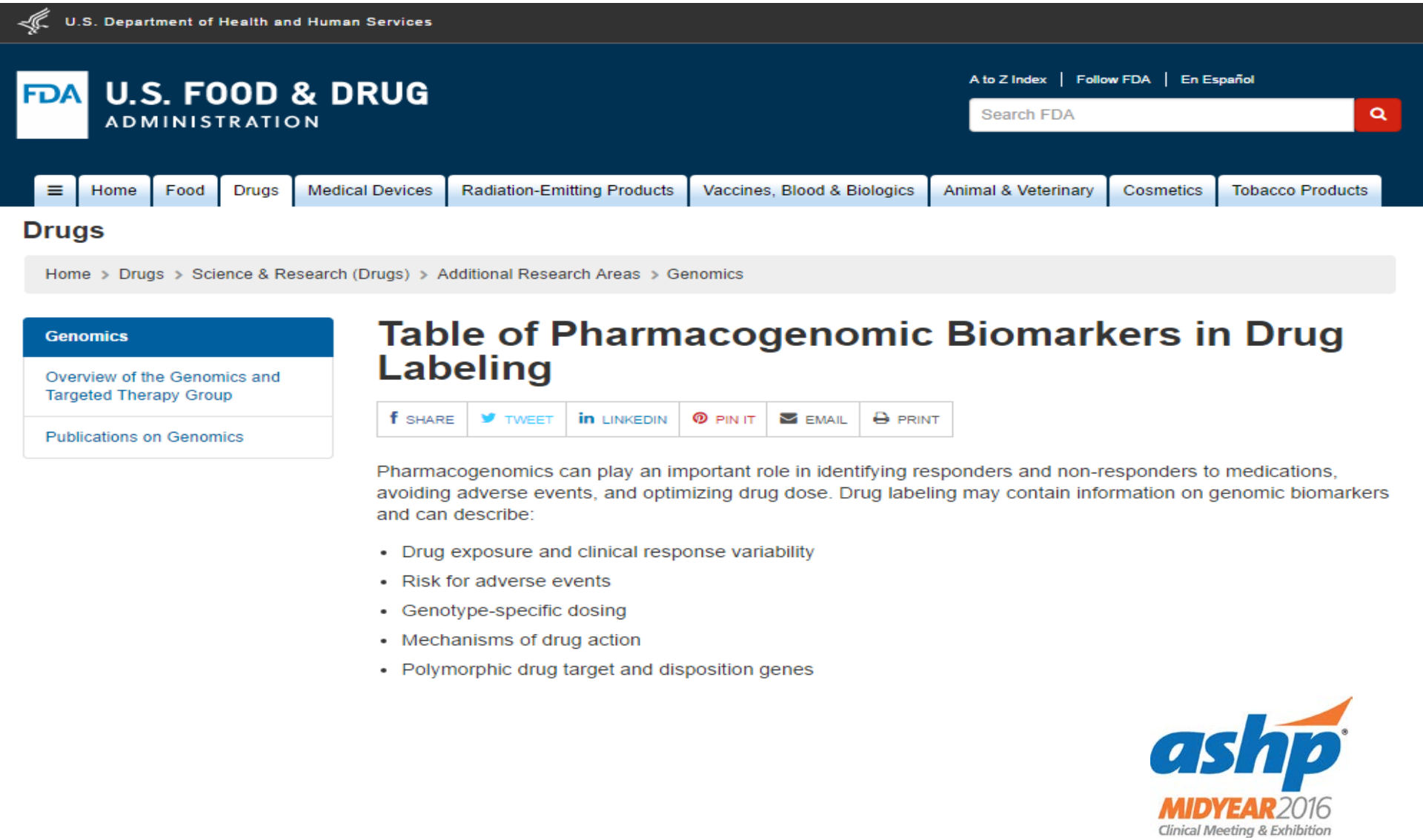
Table 5-2: Examples of clinical inhibitors for transporters (for use in clinical DDI studies and drug labeling) (9/26/2016)

Transporter	Gene	Inhibitor
P-gp[a]	*ABCB1*	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	*ABCG2*	curcumin, cyclosporine A, eltrombopag
OATP1B1, OATP1B3	*SLCO1B1*, *SLCO1B3*	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1, OAT3	*SLC22A6*, *SLC22A8*	p-aminohippuric acid (PAH)[b], probenecid, teriflunomide
MATE1, MATE2-K	*SLC47A1*, *SLC47A2*	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

Note:
Criteria for selecting in vivo inhibitors are as follows:

- P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) in vitro inhibitor.
- BCRP: (1) AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) in vitro inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.
- OATP1B1/OATP1B3: (1) AUC fold-increase ≥2 for at least one of clinical substrates in Table 2-3 with co-administration and (2) in vitro inhibitor.
- OAT1/OAT3: (1) AUC fold-increase ≥1.5 for at least one of clinical substrates in Table 2-3 with co-administration and (2) in vitro inhibitor.<./li>
- OCT2/MATE: (1) AUC fold-increase of metformin ≥ 1.5 with co-administration and (2) in vitro inhibitor.

Gene Specific Dosing



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Gene Specific Dosing

Pharmacogenomic Biomarkers in Drug Labeling

Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup‡	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alectinib	Oncology	ALK	ALK gene rearrangement positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Alirocumab	Endocrinology	LDLR	LDL receptor mutation heterozygotes	Indications and Usage, Adverse Reactions, Clinical Studies
Amitriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Anastrozole	Oncology	ESR1, PGR	Hormone receptor positive	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies
Arformoterol (1)	Pulmonary	UGT1A1	UGT1A1 poor metabolizers	Clinical Pharmacology
Arformoterol (2)	Pulmonary	CYP2D6	CYP2D6 intermediate or poor metabolizers	Clinical Pharmacology

Are We there yet?

Case

Index	Gene	SNP	Geno	Repute	Magnitude	Summary
1	ABCG2	rs2231142	(A;C)	Bad	2.1	1.74x increased gout risk; gefinitib takers 4x more susceptible to diarrhea
28	CYP2C19	rs4244285	(A;G)	Bad	3.0	poorer metabolizer of several popular medicines; patients prescribed Plavix get less benefit, and have higher risk for adverse cardiovascular events
93	SLCO1B1	rs4149056	(C;T)	Bad	2.1	reduced breakdown of some drugs; 5x increased myopathy risk for statin users

Key Takeaways

- Key Takeaway #1
  - ABC and SLC transporters are present in all humans. Expression of each transporter depends on medications, location, and genes
- Key Takeaway #2
  - Medications can induce cells to become resistant to other medications
- Key Takeaway #3
  - ABC transporters play a key role in drug-drug interactions, and with time and additional research, knowledge of ABC drug-drug interactions will become standard for all pharmacists

Questions?

Thank you for your attendance

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