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

Christopher L. Farrell, PhD
Associate Professor
Presbyterian College
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

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

- Pharmacogenetics/Pharmacogenomics
- Pharmacometabolomics
- Toxicoproteomics
- Diet
- Exercise
- Other Environmental Factors

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

Variant Allele: Alternative 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 \( \geq 1\% \) 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.

<table>
<thead>
<tr>
<th>Wild Type</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>G C A</td>
<td>G C A</td>
</tr>
<tr>
<td>1046</td>
<td>1046</td>
</tr>
<tr>
<td>C A T</td>
<td>C G T</td>
</tr>
<tr>
<td>1047</td>
<td>1048</td>
</tr>
<tr>
<td>C A T</td>
<td>C A T</td>
</tr>
<tr>
<td>1048</td>
<td>1049</td>
</tr>
<tr>
<td>G G T</td>
<td>G G T</td>
</tr>
<tr>
<td>codon #</td>
<td></td>
</tr>
</tbody>
</table>

Ala     His     His     Gly

- 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.
Genetic Variability

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

<table>
<thead>
<tr>
<th>Wild Type</th>
<th>Variant</th>
</tr>
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<tbody>
<tr>
<td>Ala</td>
<td>Gly</td>
</tr>
<tr>
<td>G C A</td>
<td>G C A</td>
</tr>
<tr>
<td>1046</td>
<td>1046</td>
</tr>
</tbody>
</table>

  | His       | His     |
  | C A T     | C A T   |
  | 1047      | 1048    |

  | Gly       | Gly     |
  | G G T     | G G A   |
  | 1049      | 1049    |

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

<table>
<thead>
<tr>
<th>Wild Type</th>
<th>Variant</th>
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</thead>
<tbody>
<tr>
<td>Arg</td>
<td>Stop (*) or X</td>
</tr>
<tr>
<td>C G G</td>
<td>C G G</td>
</tr>
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<td>1459</td>
<td>1459</td>
</tr>
</tbody>
</table>

  | Gly       | Phe     |
  | G G C     | T T T   |
  | 1460      | 1462    |

  | Lys       | Phe     |
  | A A A     | T T T   |
  | 1461      | 1462    |

  | Phe       |
  | T T T     |
  | 1462      |
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
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.
    - Ex: CYP2D6*5
Example of Genetic Variability

- CYP2D6 is a member of the cytochrome P450 superfamily responsible for playing a major role in 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

<table>
<thead>
<tr>
<th>Common Allelic Variant</th>
<th>Alterations</th>
<th>Consequences for Enzyme Activity</th>
<th>Allele Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>White</td>
</tr>
<tr>
<td>CYP2D6*2XN</td>
<td>Gene Duplication</td>
<td>Increased</td>
<td>1-5</td>
</tr>
<tr>
<td>CYP2D6*3</td>
<td>Frameshift</td>
<td>Nonfunctional</td>
<td>1-2</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>Defective Splicing</td>
<td>Nonfunctional</td>
<td>12-21</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>Gene Deletion</td>
<td>Nonfunctional</td>
<td>2-7</td>
</tr>
<tr>
<td>CYP2D6*6</td>
<td>Frameshift</td>
<td>Nonfunctional</td>
<td>1</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>Pro34Ser, Ser486Thr</td>
<td>Decreased</td>
<td>1-2</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>Thr107Ile, Arg29Cys, Ser486Thr</td>
<td>Decreased</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

- 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

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

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

Genome Browsers

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


- 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

<table>
<thead>
<tr>
<th>Variant ID</th>
<th>Chr: bp</th>
<th>Allele</th>
<th>Global MAF</th>
<th>Class</th>
<th>Source</th>
<th>Evidence</th>
<th>Clin. Sig.</th>
<th>Conseq. Type</th>
<th>AA</th>
<th>AA coord</th>
<th>SIFT</th>
<th>PolyPhen</th>
<th>Transcript</th>
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<tbody>
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<td>(+)</td>
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<td>D/N</td>
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<td>0.627</td>
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<td>(-)</td>
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<td>A/G</td>
<td>(-)</td>
<td>SNP</td>
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<td>(-)</td>
<td>SNP</td>
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<td></td>
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<td>0.009</td>
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<td>22:42127940</td>
<td>G/T</td>
<td>(-)</td>
<td>SNP</td>
<td>dbsNP</td>
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<td>Missense variant</td>
<td>R/H</td>
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<td>0.02</td>
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<tr>
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<td>0.359 (A)</td>
<td>SNP</td>
<td>dbsNP</td>
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<td>R/C</td>
<td>245</td>
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<td>0.02</td>
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<td></td>
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<tr>
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<td>G/C</td>
<td>(-)</td>
<td>SNP</td>
<td>dbsNP</td>
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<td>L/V</td>
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<tr>
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<td>A/T</td>
<td>(-)</td>
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<td>G/T</td>
<td>0.000 (T)</td>
<td>SNP</td>
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<td>0.743</td>
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<td></td>
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<td>T/C</td>
<td>(-)</td>
<td>SNP</td>
<td>dbsNP</td>
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<td>N/S</td>
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<td>(-)</td>
<td>SNP</td>
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<td>M/I</td>
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<tr>
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<td>22:42128181</td>
<td>A/T</td>
<td>0.004 (T)</td>
<td>SNP</td>
<td>dbsNP</td>
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<td>Missense variant</td>
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<td>C/A</td>
<td>(-)</td>
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<td>rs77513725</td>
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<td>C/T</td>
<td>0.004 (T)</td>
<td>SNP</td>
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<td>Missense variant</td>
<td>E/K</td>
<td>227</td>
<td>0.07</td>
<td>0.315</td>
<td>ENST0000039503</td>
<td></td>
</tr>
</tbody>
</table>

1) **rs#** (Variant ID)

2) **Variant Change** (Allele)

3) **Drug Information** (Clin. Sig.)
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
## CYP2D6 allele nomenclature

<table>
<thead>
<tr>
<th>Allele</th>
<th>Protein</th>
<th>Nucleotide changes, Gene M33358*</th>
<th>Region sequenced</th>
<th>XbaI haplotype (Rb)</th>
<th>Trivial name</th>
<th>Effect</th>
<th>Enzyme activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*1A</td>
<td>CYP2D6*1</td>
<td>None</td>
<td>29</td>
<td>M4</td>
<td>Normal</td>
<td>In vivo</td>
<td>Normal</td>
<td>Ferguson et al., 1995</td>
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<tr>
<td>CYP2D6*2A</td>
<td>CYP2D6*1</td>
<td>4828G-&gt;A</td>
<td>29</td>
<td>M4</td>
<td>Normal</td>
<td>In vitro</td>
<td>Normal</td>
<td>Liang et al., 1997</td>
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<td>CYP2D6*3A</td>
<td>CYP2D6*1</td>
<td>1573C-&gt;T</td>
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<td>Normal (a)</td>
<td></td>
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<td>Morge et al., 1998</td>
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<td>CYP2D6*1</td>
<td>2375G-&gt;A</td>
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<td></td>
<td>Normal (c)</td>
<td></td>
<td></td>
<td>Morge et al., 1998</td>
</tr>
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<td>CYP2D6*1</td>
<td>1169T-&gt;C</td>
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<td></td>
<td>Normal</td>
<td></td>
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<td>Suzuki et al., 1997</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Dogiel et al., 1996</td>
</tr>
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<td>CYP2D6*2b</td>
<td>CYP2D6*1</td>
<td>-556C-&gt;G, -1555A-G, -540C-&gt;T, A789G-&gt;A</td>
<td>29</td>
<td>CYP2D6*2</td>
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<td>Shimizu et al., 1999</td>
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<td></td>
<td>Normal (A,M,A)</td>
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</tbody>
</table>

*Contains sequencing errors: AT121216 (CYP2D6) without sequencing errors, positions after 1150 with 1 nucleotide (99196C), positions after 1150 with 2 nucleotides (2845, 183118C), and positions after 1415 with 1 nucleotide (1219, 14986C) or as compared with AT121216. CG at positions 2239-2240 should read CC. All positions in the table are numbered according to M33358.*
Gene Databases

- NAT1 & NAT2 - http://nat.mbg.duth.gr


Table of Pharmacogenomic Biomarkers in Drug Labeling

- [http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area*</th>
<th>Biomarker†</th>
<th>Referenced Subgroup‡</th>
<th>Labeling Sections‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>HLA-B*5701 allele carriers</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions</td>
</tr>
<tr>
<td>Ado-Trastuzumab</td>
<td>Oncology</td>
<td>ERBB2</td>
<td>HER2 protein overexpression or gene amplification positive</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
<tr>
<td>Emtriva</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Aflibercept</td>
<td>Oncology</td>
<td>EGFR</td>
<td>EGFR exon 10 deletion or exon 21 substitution (L858R) positive</td>
<td>Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
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<tr>
<td>Alemtropine</td>
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<td>ALK</td>
<td>ALK gene rearrangement positive</td>
<td>Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
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<td>Alirocumbine</td>
<td>Endocrinology</td>
<td>LDLR</td>
<td>LDL receptor mutation heterozygotes</td>
<td>Indications and Usage, Adverse Reactions, Clinical Studies</td>
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<td>Amitriptyline</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>CYP2D6 poor metabolizers</td>
<td>Precautions</td>
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<tr>
<td>Anastrozole</td>
<td>Oncology</td>
<td>ESR1, PGR</td>
<td>Hormone receptor positive</td>
<td>Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies</td>
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<tr>
<td>Arformoterol (1)</td>
<td>Pulmonary</td>
<td>UGT1A1</td>
<td>UGT1A1 poor metabolizers</td>
<td>Clinical Pharmacology</td>
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<tr>
<td>Arformoterol (2)</td>
<td>Pulmonary</td>
<td>CYP2D6</td>
<td>CYP2D6 intermediate or poor metabolizers</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Artipiprazole</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>CYP2D6 poor metabolizers</td>
<td>Dosage and Administration, Use in Specific Populations, Drug Interactions, Clinical Pharmacology</td>
</tr>
</tbody>
</table>
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).


- 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
PharmGKB

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

Available Guidelines

1. CPIC Guideline for amitriptyline and CYP2C19, CYP2D6
2. CPIC Guideline for clomipramine and CYP2C19, CYP2D6
3. CPIC Guideline for codeine and CYP2D6
4. CPIC Guideline for desipramine and CYP2D6
5. CPIC Guideline for doxepin and CYP2C19, CYP2D6
6. CPIC Guideline for fluoxetine and CYP2D6
7. CPIC Guideline for imipramine and CYP2C19, CYP2D6
8. CPIC Guideline for nortriptyline and CYP2D6
9. CPIC Guideline for paroxetine and CYP2D6
10. CPIC Guideline for trazodone and CYP2C19, CYP2D6
11. DPWG Guideline for amitriptyline and CYP2D6
12. DPWG Guideline for arbidol and CYP2D6
13. DPWG Guideline for atomoxetine and CYP2D6
14. DPWG Guideline for carvedilol and CYP2D6
15. DPWG Guideline for clomipramine and CYP2D6
16. DPWG Guideline for clozapine and CYP2D6
17. DPWG Guideline for codeine and CYP2D6
18. DPWG Guideline for doxepin and CYP2D6
19. DPWG Guideline for duloxetine and CYP2D6
20. DPWG Guideline for flecainide and CYP2D6
PharmGKB

3. CPIC Guideline for codeine and CYP2D6

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

Pick alleles for CYP2D6: *4 ▼ ▼

There's more of this guideline. Read more.

4. CPIC Guideline for desipramine and CYP2D6

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

There's more of this guideline. Read more.

5. CPIC Guideline for doxepin and CYP2D6

Summary
Tricyclic antidepressants have complex pharmacokinetic properties; it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2D6 to other tricyclics including doxepin. In the guideline for amitriptyline, an alternative drug is recommended for CYP2D6 or CYP2C19 poor metabolizers. 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

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.
### 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.

### Metabolizer Status
Poor metabolizer

### Implications
Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief

### Activity Score
0

### 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
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.
PharmGKB Curated Pathways

1. Acetaminophen Pathway (therapeutic doses, Pharmacokinetics)
   Stylized diagram showing acetaminophen metabolism and transport in the liver.

2. Acetaminophen Pathway (therapeutic doses, Pharmacokinetics)
   Stylized diagram showing acetaminophen metabolism at higher acetaminophen doses (toxic doses) in the liver.

3. Acetaminophen CYP450 2D6 Metabolism Pathway, Pharmacokinetics
   Drug-specific representation of the candidate genes involved in Transport, metabolism and clearance.

4. Baricitinib Pathway, Pharmacometrics

5. Ceftepime Pathway, Pharmacokinetics

6. Ceftepime Pathway, Pharmacokinetics
   Pharmacokinetics of the selective serotonin reuptake inhibitor ceftepime.

7. Dapagliflozin Pathway, Pharmacokinetics
   Pharmacokinetics of the sodium-glucose cotransporter 2 inhibitor dapagliflozin.

8. Codeine and Morphine Pathway, Pharmacometrics
   Representation of the candidate genes involved in metabolism of codeine and morphine.

9. Cephalosporin Pathway, Pharmacokinetics
   Pharmacokinetics of the cephalosporin antibiotic.

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

- References
- Other databases/gene browsers
  - NCBI
  - Ensembl
  - Online Mendelian Inheritance in Man (OMIM)
  - GeneCard
Specialized Pharmacogenomic & Other Related Websites


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

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

Part 2

Eddie Grace, Pharm.D.,BCPS(AQ-ID),AAHIVP
Vice Chair/Associate Professor of Clinical and Administrative Sciences
Notre Dame of Maryland University
School of Pharmacy
Baltimore, MD
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”? 

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:
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 rosvastatin. [See Clinical Pharmacology (12.3).]
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
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Location</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC22A1</td>
<td>OCT1</td>
<td>Liver</td>
<td>Thiamine, acetylcholine, metformin, acyclovir, lamivudine, pentamidine, palitacel, and oxaliplatin</td>
</tr>
<tr>
<td>SLC22A2</td>
<td>OCT2</td>
<td>Kidney</td>
<td>Creatinine, bile acids, acetylcholine, norepinephrine, serotonin, metformin, pindolol, propranolol, ranitidine, cisplatin, famotidine, lamivudine, and procanimide</td>
</tr>
<tr>
<td>SLA22A3</td>
<td>OCT3</td>
<td>Kidney, liver, placenta, heart, and skeletal muscle</td>
<td>Creatinine, acetylcholine, dopamine, norepinephrine, serotonin, histamine, progesterone, testosterone, lidocaine, atropine, prazosin, metformin, ranitidine, verapamil, mitoxantrone, and lamivudine</td>
</tr>
<tr>
<td>SLC22A4-5</td>
<td>OCTN</td>
<td>Ubiquitously expressed</td>
<td>Acetylcholine, pregabalin, tiotropium, doxorubicin, etoposide, verapamil</td>
</tr>
<tr>
<td>SLC22A6</td>
<td>OAT</td>
<td>Kidney&gt;liver and brain</td>
<td>Adefovir, zidovudine, cipro, methotrexate, pravastatin, antibiotics, NSAIDS, diuretics</td>
</tr>
</tbody>
</table>

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
Theodoulou F. Biochem Soc. Trans 2015;43:1033-1039
<table>
<thead>
<tr>
<th>Human ABC-Family</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>G</th>
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<tr>
<td>Transporter Topology</td>
<td>![Diagram A]</td>
<td>![Diagram B]</td>
<td>![Diagram C]</td>
<td>![Diagram D]</td>
<td>![Diagram G]</td>
</tr>
<tr>
<td>Lipophilic Substrates</td>
<td>(Phospho)lipids (A1, A3, A4, A7, A12) Sphingomyelin (A1, A3) Cholesterol (A1, A2, A5)</td>
<td>Phospholipids (B1, B4) Sphingolipids (B1) Bile salts (B11) Drugs (B1)</td>
<td>Phospholipids (C1) Bile salts (C1, C2, C3) Steroids (C1, C10) Drugs (C1, C2)</td>
<td>(VLC)FA (D1-D4)</td>
<td>Lipids (G4) Cholesterol (G1, G4, G5/G8) Steroids (G2, G5/G8) Drugs (G2)</td>
</tr>
</tbody>
</table>
ABC Transporter Locations

Foods/phytochemicals

Interaction with blood-brain barrier transporters can affect drug distribution into brain

Interaction with hepatic transporters can affect hepatic uptake and biliary excretion of drugs

Interaction with intestinal transporters can affect drug absorption and bioavailability

Interaction with renal transporters can affect drug excretion

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

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, sparrafloxacine, 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**: curcuminoinds, 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, grepafloxacin, 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

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Chen Z. Cancer Letters 2016;370:153-164
## ABC Transporters and Diseases

<table>
<thead>
<tr>
<th>ABC transporter</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA1</td>
<td>Tangier disease and familial high density lipoprotein (HDL) deficiency;</td>
</tr>
<tr>
<td></td>
<td>atherosclerosis; Alzheimer’s disease</td>
</tr>
<tr>
<td>ABCA3</td>
<td>Neonatal surfactant deficiency and pulmonary fibrosis; congenital cataract</td>
</tr>
<tr>
<td>ABCA4</td>
<td>Stargardt macular degeneration</td>
</tr>
<tr>
<td>ABCA7</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ABCA12</td>
<td>Harlequin and lamellar ichthyosis</td>
</tr>
<tr>
<td>ABCB1/transporter associated with antigen processing (Tap)2; ABCB2/Tap1</td>
<td>Immune deficiency; arthritis risk</td>
</tr>
<tr>
<td>ABCB4/MDR2</td>
<td>PFIC3; other types of cholestasis</td>
</tr>
<tr>
<td>ABCB7</td>
<td>Sideroblastic anaemia and ataxia</td>
</tr>
<tr>
<td>ABCB11/bile salt export pump (BSEP)</td>
<td>PFIC2; intrahepatic cholestasis of pregnancy; neonatal respiratory distress syndrome</td>
</tr>
<tr>
<td>ABCCC2/MPR2</td>
<td>Dubin-Johnson syndrome</td>
</tr>
<tr>
<td>ABCCC5/MPR5</td>
<td>Inherited hypertrichosis</td>
</tr>
<tr>
<td>ABCCC6/MPR6</td>
<td>Pseudoxanthoma elasticum</td>
</tr>
<tr>
<td>ABCCC7/CFTR</td>
<td>CF</td>
</tr>
<tr>
<td>ABCCC8/SUR1</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ABCCC9/SUR2</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ABCD1/adrenoleukodystrophy protein (ALDP)</td>
<td>X-linked adrenoleukodystrophy</td>
</tr>
<tr>
<td>ABCD3/peroxisome membrane protein (PMP70)</td>
<td>X-linked adrenomyeloneuropathy</td>
</tr>
<tr>
<td>ABCD4/PMP69</td>
<td>Hepatosplenomegaly; liver disease</td>
</tr>
<tr>
<td>ABCG2/breast cancer resistance protein (BCRP)</td>
<td>Inborn error of vitamin B12 metabolism</td>
</tr>
<tr>
<td>ABCG5; ABCG8</td>
<td>Gout and hyperuricaemia</td>
</tr>
<tr>
<td>ABCB1/P-gp, ABCC1/MPR1, ABCG2/BCRP</td>
<td>Sitosterolemia; coronary heart disease; gallstone disease</td>
</tr>
<tr>
<td>ABCC2-6</td>
<td>Multi-drug resistance</td>
</tr>
<tr>
<td></td>
<td>Drug transport</td>
</tr>
</tbody>
</table>
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)].
Based on the known information, which one of the following is the most appropriate course of action?

A. Increase rosvastatin dose
B. Decrease rosvastatin dose by ~50%
C. Continue current rosvastatin 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
  - 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

- Overview
- Background Information
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Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

- CYP Enzymes
  - In vitro
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  - Clinical index drugs
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    - Clinical index inhibitors
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    - Clinical substrates
    - Clinical inhibitors
    - Clinical inducers
- Transporters
  - In vitro
    - In vitro substrates
    - In vitro inhibitors
  - Examples of clinical substrates, inhibitors and inducers
    - Clinical substrates
Table 5-1: Examples of clinical substrates for transporters (for use in clinical DDI studies and/or drug labeling) (9/26/2016)

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

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)

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

**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.
- **OCT2/MATE:** (1) AUC fold-increase of metformin ≥ 1.5 with co-administration and (2) in vitro inhibitor.
Gene Specific Dosing

Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes
Gene Specific Dosing

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

<table>
<thead>
<tr>
<th>Index</th>
<th>Gene</th>
<th>SNP</th>
<th>Geno</th>
<th>Repute</th>
<th>Magnitude</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ABCG2</td>
<td>rs2231142</td>
<td>(A;C)</td>
<td>Bad</td>
<td>2.1</td>
<td>1.74x increased gout risk; gefinitib takers 4x more susceptible to diarrhea</td>
</tr>
<tr>
<td>28</td>
<td>CYP2C19</td>
<td>rs4244285</td>
<td>(A;G)</td>
<td>Bad</td>
<td>3.0</td>
<td>poorer metabolizer of several popular medicines; patients prescribed Plavix get less benefit, and have higher risk for adverse cardiovascular events</td>
</tr>
<tr>
<td>93</td>
<td>SLC01B1</td>
<td>rs4149056</td>
<td>(C;T)</td>
<td>Bad</td>
<td>2.1</td>
<td>reduced breakdown of some drugs; 5x increased myopathy risk for statin users</td>
</tr>
</tbody>
</table>
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

Eddie Grace, Pharm.D., BCPS(AQ-ID), AAHIVP
EGrace@ndm.edu/DrEddie@ufl.edu