Pharmacogenetics: Clinical Application of Population and Individual Pharmacogenetic Data

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**Disclosure and Conflict of Interest**

**General:**

- David F. Kisor, BS, PharmD, is a pharmacogenomics education consultant to PWNHealth, LLC and Millennium Health, LLC.

Listed as resource among others (Slide 51):


*receive royalties from the sales of this textbook.*
Pharmacist Objectives

At the conclusion of this program, the pharmacist will be able to:

1. Describe the basic theory of pharmacogenetics as it relates to the practice of pharmacy.

2. Discuss strategies to implement pharmacogenetic testing in different practice settings.

3. Develop a clinical recommendation for drug therapy based on pharmacogenetic data for a specific patient case.
Technician Objectives

At the conclusion of this program, the pharmacy technician will be able to:

1. Define pharmacogenomics
2. Describe how differences in pharmacogenomics may affect drug therapy
3. List common drugs impacted by differences in pharmacogenomics amongst patients
Pre-Test Questions

• How does pharmacogenetics compare/differ to/from pharmacogenomics?
• What are the pharmacogenetic genes/proteins of interest?
• What is the importance of a patient’s phenotype relative to drug therapy?
Definitions

**Pharmacogenetics** (PGt) - The study of a gene involved in response to a drug.

**Pharmacogenomics** (PGx) - The study of many genes, in some cases, the entire genome, involved in response to a drug.

Kisor DF, Kane MD, Talbot JN, Sprague JE. *Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine*. JBL 2014
Definitions

*Single Nucleotide Polymorphism (SNP)* - A variant DNA sequence in which a single nucleotide has been replaced by another base.

e.g., T>C

*Haplotype* - A series of polymorphisms (e.g., SNPs) which are inherited together.

Kisor DF, Kane MD, Talbot JN, Sprague JE. *Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine*. JBL 2014
“Pharmacogenetic Genes”

Question 2

Product - Receptors

Examples: Histamine, β₂-adrenergic

Kisor DF, Kane MD, Talbot JN, Sprague JE. *Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine*. JBL 2014
“Pharmacogenetic Genes”

Question 2

Product - Transporters

Examples:

P-glycoprotein

OATP1B1

“Pharmacogenetic Genes”

Product - Drug Metabolizing Enzymes

Examples: CYP450s, TPMT

Wild-Type “Common” Forms of Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Product</th>
<th>Wild-Type</th>
<th>Common Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLCO1B1</td>
<td>Transporter</td>
<td>*1A</td>
<td>*1A/*1A</td>
<td>Normal</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>DME</td>
<td>*1</td>
<td>*1/*1</td>
<td>Normal (extensive)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>DME</td>
<td>*1</td>
<td>*1/*1</td>
<td>Normal (extensive)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>DME</td>
<td>*1</td>
<td>*1/*1</td>
<td>Normal (extensive)</td>
</tr>
<tr>
<td>NAT2</td>
<td>DME</td>
<td>*4</td>
<td>*4/*4</td>
<td>Normal (extensive)</td>
</tr>
</tbody>
</table>

# Genetic Variation - Drug Transporter

<table>
<thead>
<tr>
<th>Gene</th>
<th>Transporter</th>
<th>Variant (allele)</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLCO1B1</td>
<td>OATP1B1</td>
<td>*15</td>
<td>Decreased influx (uptake)</td>
</tr>
</tbody>
</table>

## Genetic Variation - Drug Metabolizing Enzymes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Enzyme</th>
<th>Variant (allele)</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>*2</td>
<td>Decreased function</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>*3</td>
<td>Decreased function</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>*2</td>
<td>Loss-of-function</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>*17</td>
<td>Increased function</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>*2</td>
<td>Normal function</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>*2xN</td>
<td>Increased function</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>*4</td>
<td>Increased function</td>
</tr>
<tr>
<td>TPMT</td>
<td>TPMT</td>
<td>*3A</td>
<td>Decreased function</td>
</tr>
</tbody>
</table>

Frequency of Genetic Variation - *SLCO1B1*

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasian</th>
<th>South/ Central America</th>
<th>African</th>
<th>Middle Eastern</th>
<th>Asian</th>
<th>SW Asian</th>
<th>Oceania</th>
</tr>
</thead>
<tbody>
<tr>
<td>*5</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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</tbody>
</table>

*5 - rs4149056 c.521T>C; V174A

Frequency of Genetic Variation - *SLCO1B1*

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasian</th>
<th>South/ Central America</th>
<th>African</th>
<th>Middle Eastern</th>
<th>Asian</th>
<th>SW Asian</th>
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</tr>
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<td>*5</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
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</tr>
<tr>
<td>*15</td>
<td>0.14</td>
<td>0.24</td>
<td>0.03</td>
<td>0.15</td>
<td>0.13</td>
<td>0.06</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*5 - rs4149056 c.521T>C; V174A  
*15 - rs4149056 c.521T>C; V174A and rs2306283 c.492A>G; N130D

## Frequency of Genetic Variation - CYP2C9

<table>
<thead>
<tr>
<th>Allele</th>
<th>White</th>
<th>Asian</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>0.13</td>
<td>0.00</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*2 - rs1799853 C>T; R144C

Frequency of Genetic Variation - CYP2C9

<table>
<thead>
<tr>
<th>Allele</th>
<th>White</th>
<th>Asian</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>0.13</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td>*3</td>
<td>0.07</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*2 - rs1799853 C>T; R144C  
*3 - rs1057910 A>C; I359L

Frequency of Genetic Variation - CYP2C19

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>American</th>
<th>East Asian</th>
<th>European</th>
<th>Middle Eastern</th>
<th>Oceanian</th>
<th>South/ Central Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>0.15</td>
<td>0.12</td>
<td>0.29</td>
<td>0.15</td>
<td>0.12</td>
<td>0.61</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*2 - rs4244285 c.681G>A; Splicing defect

## Frequency of Genetic Variation - CYP2C19

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>American</th>
<th>East Asian</th>
<th>European</th>
<th>Middle Eastern</th>
<th>Oceanian</th>
<th>South/Central Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>0.15</td>
<td>0.12</td>
<td>0.29</td>
<td>0.15</td>
<td>0.12</td>
<td>0.61</td>
<td>0.35</td>
</tr>
<tr>
<td>*17</td>
<td>0.16</td>
<td>0.18</td>
<td>0.027</td>
<td>0.21</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*2 - rs4244285 c.681G>A; Splicing defect  
*17 - rs12248560 c.-806C>T; Increased expression

**Frequency of Genetic Variation - CYP2D6**

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>African American</th>
<th>Caucasian</th>
<th>Middle Eastern</th>
<th>East Asian</th>
<th>South/ Central Asian</th>
<th>Americas</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2xN</td>
<td>0.064</td>
<td>0.016</td>
<td>0.022</td>
<td>0.049</td>
<td>0.015</td>
<td>0.012</td>
<td>0.024</td>
</tr>
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</table>

*2xN - Increased expression (multiple copies of the gene)

### Frequency of Genetic Variation - CYP2D6

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>African American</th>
<th>Caucasian</th>
<th>Middle Eastern</th>
<th>East Asian</th>
<th>South/ Central Asian</th>
<th>Americas</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2xN</td>
<td>0.064</td>
<td>0.016</td>
<td>0.022</td>
<td>0.049</td>
<td>0.015</td>
<td>0.012</td>
<td>0.024</td>
</tr>
<tr>
<td>*4</td>
<td>0.034</td>
<td>0.06</td>
<td>0.18</td>
<td>0.076</td>
<td>0.005</td>
<td>0.066</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*2xN - Increased expression (multiple copies of the gene)

*4 - rs1065852 100C>T; P34S

## Frequency of Genetic Variation - *TPMT*

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasian</th>
<th>Mediterranean</th>
<th>South American</th>
<th>African</th>
<th>Middle Eastern</th>
<th>Mexican</th>
<th>Asian</th>
<th>SW Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>*3A</td>
<td>0.04</td>
<td>0.03</td>
<td>0.03</td>
<td>0.0022</td>
<td>0.01</td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*3A - C>T at rs#1800460, T>C at rs#1142345

Drug Selection Algorithm

Clinical Pharmacogenetics Implementation Consortium (CPIC)

Considering antiplatelet therapy with clopidogrel for ACS/PCI

\[ \text{CYP2C19 genotype results} \]

- **UM** (*1/*17, *17/*17)
  - Standard dosing of clopidogrel
- **EM** (*1/*1)
- **IM** (*1/*2, *1/*3, *2/*17)
  - Consider alternative antiplatelet agent (e.g., prasugrel, ticagrelor)
- **PM** (*2/*2, *2/*3, *3/*3)

Phenotype - An individual’s expression of a physical trait or physiologic function due to genetic makeup and environmental and other factors.


Drug Selection Algorithm

Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Considering antiplatelet therapy with clopidogrel for ACS/PCI
- CYP2C19 genotype results
  - UM (*1/*17, *17/*17)
  - EM (*1/*1)
  - IM (*1/*2, *1/*3, *2/*17)
  - PM (*2/*2, *2/*3, *3/*3)

- Standard dosing of clopidogrel
- Consider alternative antiplatelet agent (e.g., prasugrel, ticagrelor)

Case 1: Clopidogrel-\textit{CYP2C19}

Benjamin is 39 y.o. WM who presents to the ER with a chief complaint of chest pain at rest. EKG indicated ST segment elevation and Benjamin received percutaneous coronary intervention (PCI) with stent placement in two of his coronary arteries. At the time of PCI, Benjamin provided a DNA sample via cheek swab for testing of his \textit{CYP2C19} genotype.

Benjamin received a 60 mg loading dose of prasugrel in the catheterization lab and was given a prescription for a seven day supply of prasugrel 10 mg. What suggestion would you have regarding Benjamin’s antiplatelet therapy?
MTM - DNA Sampling

- Confirm patient has not eaten within 30 minutes
- Confirm patient has not had CYP2C19 genotyping prior
- Confirm ACS with PCI

- Perform buccal swab
- Send to lab
- Lab results reported

### CYP2C19 Genotype Results

**Component Results**

<table>
<thead>
<tr>
<th>MISC. #1 REFERENCE GROUP TEST: SEE BELOW</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment:</td>
<td></td>
</tr>
<tr>
<td>Test name</td>
<td>Result</td>
</tr>
<tr>
<td>RefRange</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2C19 Specimen</th>
<th>Whole Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Allele 1</td>
<td>*1</td>
</tr>
<tr>
<td>CYP2C19 Allele 2</td>
<td>*17</td>
</tr>
</tbody>
</table>

**CYP2C19 Gene Mutation Interpretation:** See Note

**Indication for testing:** Assess genetic risk for impaired CYP2C19-mediated drug metabolism.

**Recommendations:** Consultation with a clinical pharmacy professional to discuss drug and dose selection is recommended. Detection of allelic variants does not replace the need for therapeutic drug and clinical monitoring as pharmacokinetics and drug response may be affected by other genetic and non-genetic factors.

Kisor DF. Communication from ARUP clinical laboratories. 2/8/2013.
MTM - DNA Sampling

- Confirm patient has not eaten within 30 minutes
- Confirm patient has not had \textit{CYP2C19} genotyping prior
- Confirm MI with PCI

- Perform buccal swab
- Send to lab
- Lab results reported
- Interpretation of genetic testing results
- Therapeutic/economic recommendation
Drug Selection Algorithm - Reactive

Clinical Pharmacogenetics Implementation Consortium (CPIC)

**Preemptive Population-Based**

What if BR was of Oceanian descent visiting from Australia?

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
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<th>Middle Eastern</th>
<th>Oceanian</th>
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</thead>
<tbody>
<tr>
<td>*2</td>
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<td>*17</td>
<td>0.16</td>
<td>0.18</td>
<td>0.027</td>
<td>0.21</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Case 2: Metoprolol-CYP2D6

Samuel is a 30 year old male with hypertension. He is receiving metoprolol succinate 100 mg once daily. Samuel is now started on fluoxetine for treatment of depression. Two days after starting on the fluoxetine, the patient is seen at the emergency room, having suffered a fractured arm after getting “dizzy” and falling. As part of his discharged process, the ER pharmacist is asked to provide medication counseling.
Pharmacist recommends genetic testing

- Samuel states as a “techie”, he had provided a direct-to-consumer company (DTC) his saliva for DNA analysis. Samuel gets the results from his smart phone, telling the pharmacist that he is a CYP2D6*4/*10 individual, “Whatever that means.”

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Consequences</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*4/*10</td>
<td>IM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What are the consequences of the \textit{CYP2D6\^{*}4/\^{*}10} genotype/IM phenotype in a patient taking metoprolol?

a. Decreased CL  
b. Increased AUC  
c. Increased half-life  
d. a and c above  
e. a, b, and c above
What are the consequences of the CYP2D6*4/*10 genotype/IM phenotype in a patient taking metoprolol?

a. Decreased CL
b. Increased AUC
c. Increased half-life
d. a and c above
e. a, b, and c above
Drug-Gene Interaction Influence

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Consequences</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*4/*10</td>
<td>IM</td>
<td>↓ CL, ↑ AUC, ↑ t½</td>
<td>Still to come...</td>
</tr>
</tbody>
</table>

The administration of a drug to an individual who carries at least one variant form of a gene that codes for the enzyme that metabolizes the drug.
What are the consequences of the CYP2D6*4/*10 genotype/IM phenotype in a patient taking metoprolol?

- a. Decreased CL
- b. Increased AUC
- c. Increased half-life
- d. a and c above
- e. a, b, and c above
What are the consequences of the addition of fluoxetine in a patient taking metoprolol?

- a. Decreased CL
- b. Increased AUC
- c. Increased half-life
- d. a and c above
- e. a, b, and c above
# Drug-Drug Interaction Influence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacting Drug</th>
<th>Consequences</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Metoprolol    | Fluoxetine       | ↓ CL  
↑ AUC  
↑ t½          | Still to come...   |
What are the consequences of the CYP2D6*4/*10 genotype/IM phenotype and the addition of fluoxetine in a patient taking metoprolol?

a. ↓ CL
b. ↑ AUC
c. ↑ half-life
d. ↓ ↓ CL
e. ↑ ↑ AUC
f. ↑ ↑ half-life
g. a, b, and c above
h. d, e, and f above
What are the consequences of the CYP2D6*4/*10 genotype/IM phenotype and the addition of fluoxetine in a patient taking metoprolol?

a. ↓ CL
b. ↑ AUC
c. ↑ half-life
d. ↓ ↓ CL
e. ↑ ↑ AUC
f. ↑ ↑ half-life
g. a, b, and c above
h. d, e, and f above
Drug-Drug-Gene Interaction

The addition of an inhibitor or inducer of a drug metabolizing enzyme in an individual receiving a drug metabolized by a variant form of that enzyme.

- Drug-gene interaction: metoprolol/CYP2D6 *4/*10 - IM
- Drug-drug interaction: metoprolol/fluoxetine - Δ to PM
- Drug-drug-gene interaction = phenoconversion
Genetic and Drug Interaction Influence

<table>
<thead>
<tr>
<th>Genotype Drug</th>
<th>Phenotype Interacting Drug</th>
<th>Consequences</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*4/*10 Metoprolol</td>
<td>IM Fluoxetine</td>
<td>↓↓ CL ↑↑ AUC ↑↑ t½ Phenoconversion: IM&gt;PM</td>
<td>Choose an alternative antihypertensive</td>
</tr>
</tbody>
</table>
Abigail was born this morning at 5:43 AM at The Ohio State University Hospital. This healthy newborn had a heel prick performed for amino acid disorders, endocrine disorders, fatty acid oxidation, among other newborn screenings. Additionally the sample is forwarded to the lab for genetic sequencing.

Forward 26 years, when Abigail is rushed to the Cleveland Clinic by her husband, Jackson, where she will deliver her first child. Complications require a Cesarean Section be performed, which results in the birth of a healthy daughter, named Zeta. Post-Cesarean section, Abigail is started on Tylenol #3 for pain.
Zeta begins breastfeeding within 12 hours and appears to be thriving. Both mother and child are discharged from the hospital at 36 hours. Two days later, Zeta is brought to the new infants clinic as she is drowsy, lethargic and does not respond to stimulation. Zeta is immediately admitted to the children’s hospital. Abigail also appears drowsy and is slow to respond, with slurred speech.
How could the DNA sequencing have impacted this situation?

- It could identify potential drug-gene interactions in the mother

- It could identify potential drug-gene interactions in the baby
**Codeine-CYP2D6**

**Codeine**
- Prodrug converted to morphine via CYP2D6

**CYP2D6**
- Gene coding for the CYP2D6 metabolizing enzyme
- Frequency of CYP2D6 Phenotypes:

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Frequency</th>
<th>Example Diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM</td>
<td>1-2%</td>
<td>*1/*1xN, *1/*2xN</td>
</tr>
<tr>
<td>IM</td>
<td>2-11%</td>
<td>*4/*10, *5/*41</td>
</tr>
<tr>
<td>PM</td>
<td>5-10%</td>
<td>*4/*4, *4/*5, *5/*5, *4/*6</td>
</tr>
</tbody>
</table>

A query of Abigail’s DNA sequencing data (stored securely in a database) reveals that she is a UM having a *1/*1xN genotype, meaning she has multiple copies (≥2) of genes that code for active CYP2D6 enzymes.

At this point, the Tylenol #3 is discontinued and an alternative pain medication is prescribed (e.g., ibuprofen)
How could the DNA sequencing have impacted this situation?

- Codeine would have been considered at a lower dose.
- Hydrocodone would have been considered.
- A non-opioid would have been considered.
- Morphine would have been considered.
- Tramadol would have been considered.

Which of the above would be appropriate?
Current Limitations of PGt Testing

- Lack of PGt education
  - CE programs, Certification programs*, ACPE Standards
- Lack of reimbursement
  - CMS LCD improving:
    - CYP2C19-clopidogrel in ACS/PCI population
    - CYP2D6-amitriptyline, nortriptyline, tetrabenazine
    - CYP2C9-warfarin (in study settings)
- Testing turn-around time
  - Within hours in some research/academic settings
  - 3-5 days typical
- Health information technology
- Ethical, legal, and social implications
• Incorporation with MTM services
• Incorporation with TDM services
• Others
Books:

- Pharmacogenomics: Applications to Patient Care, 3rd Edition. ACCP 2015.
- Others

CE:

- Online certification program: RxGenomix.com
- Others

Examples in Practice:

- Others
Pharmacogenomics is another “piece of the puzzle” to be considered with other patient information.

Pharmacists are the providers with the most appropriate background to apply pharmacogenomics to patient care.
Questions?
Speaker Contact Information

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