Pharmacogenomics in Current Practice

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Objectives

• Review the concept of pharmacogenetics and pharmacogenomics
• Discuss how genetics affect the activity of drug metabolizing enzymes
• Discuss examples of how pharmacogenetics and pharmacogenomics will lead to individualization of drug therapy
• Identify resources for obtaining current and updated pharmacogenomics information

Clinical Problem

“The vast majority of drugs – more than 90% - only work in 30 or 50 per cent of the people...Drugs out there on the market work, but they don’t work in everybody” Allen Roses, vice president at GlaxoSmithKline

What if there were a way...

• ...to know if a depressed patient would respond to an antidepressant—before it was prescribed?
• ...to predict if a patient will have analgesia with morphine or codeine?

In recent years, advances in genetic testing have made such drug-response predictions possible for patients with certain gene variants

A new initiative ON PRECISION MEDICINE

• “Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”
  — President Barack Obama, State of the Union Address, January 20, 2015
• $1.50 million to NIH for development of a voluntary national research database
• $70 million to the National Cancer Institute (NCI)
• $10 million to FDA to acquire additional expertise and advance the development of high-quality, curated databases to support the regulatory structure needed to advance innovation in precision medicine and protect public health.
• $5 million to Office of the National Coordinator for Health Information Technology (ONC) to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems.

https://obamawhitehouse.archives.gov/node/333101
Accessed November 27, 2017
Pharmacogenetics vs. Pharmacogenomics

- **Genetics**: study of genetic causes of individual variations in drug response. Limited to the effects of one or a few genes.
- **Genomics**: study of the genome-wide role of human variation in drug response. Includes:
  - pharmacogenetic effects
  - the application of genomic technologies in drug discovery, disposition, and function

American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group

Goal of Pharmacogenomics

- Optimize drug therapy
  - Maximize effectiveness
  - Minimize toxicity
  - Minimize pharmacokinetic and pharmacodynamic variability of drug therapy
  - Avoid unnecessary treatment
  
  “The right drug, right dose, to the right person”

Question #1

What is pharmacogenomics?
A. Branch of pharmacology that studies genes in drug safety
B. Branch of pharmacology that studies genes in drug efficacy
C. Branch of pharmacology that allows drug dosing and selection based on genetic makeup of the individual
D. All of the above

Pharmacogenomic Nomenclature

- **Polymorphism**: variation in DNA sequence
  - Base change frequency > 1% of population
  - Single Nucleotide Polymorphism (SNP or “snips”)
  - Changes in more than 1 nucleotide
  - Entire gene insertion, deletion, or extra copies of a gene
- **Mutation**: base change frequency < 1% of population

Understanding the effect of genetic polymorphism

- Identify the polymorphism
- What can be affected by the polymorphism?
  - Drug metabolizing enzyme
  - Drug transporter
  - Drug target
  - Disease
  - Or no functional effect
- Who is impacted?
  - Individual vs population
- How does it affect a drug?
  - Pharmacokinetic or pharmacodynamic effect
  - Dosing, efficacy, toxicity
  - No effect on a drug
- How does it affect a disease?
  - Increase or decrease susceptibility
  - Utility as screening or diagnostic tool

Allele – a variant or wild type form of a gene at a particular location on a chromosome

Allele nomenclature example: VKORC1 1173 C > T
(Does not distinguish if this is a wild type or variant)

Gene

Nucleotide position within sequence of gene

Original "Wild-type" nucleotide

Variant nucleotide

Examples of allele nomenclature:

VKORC1*1 (VKORC1)
VKORC1*2 (VKORC1 681 G > A)
VKORC1*3 (VKORC1 636 G > A)

The * (star) and number after the gene designate the allele


"Star" Nomenclature (describes alleles)

- Example 1: CYP2C19 (function varies based on the allele)
  - *1 = always indicate wild type allele (normal) enzymatic activity
  - *2 = NO enzyme activity
  - *3 = NO enzyme activity

- Example 2 for another enzyme: CYP2D6
  - *1 = always indicate wild type allele (normal) enzymatic activity
  - *2 = Decreased enzyme activity
  - *3 = Decreased enzyme activity

Keypoint: Function of each gene varies based on the allele.

- Allele nomenclature may look exactly the same for different genes; but may have different functional outcomes, depending on specific gene/protein


Genotype Nomenclature
(Refers to the 2 alleles inherited for a specific gene)

- Example for CYP2C19
  - An individual may carry 2 copies of *2 allele (CYP2C19*2/*2)
- Genotypes may impact drug metabolism
  - CYP2C19*1/*1 = wild type enzyme activity
  - CYP2C19*1/*2 or *1/*3 – reduced enzyme activity
  - CYP2C19*2/*2 or *2/*3 or *3/*3 = no enzyme activity


Polymorphism Types

- Single Nucleotide Polymorphism (SNP)
  - A single base substitution occurring within a gene
  - Several million identified
  - May or may not alter protein synthesis
- Coding SNP
  - Synonymous
  - Non-synonymous
  - Premature stop codon

- Other types of polymorphism (hundreds or thousands of nucleotides may be involved)
  - Gene deletion
  - Copy number variant


Coding Region SNPs

- Synonymous
- Non-Synonymous
  - Missense – amino acid change
  - Nonsense – changes amino acid to stop codon.

Synonymous Codon SNP

- **Example:** P-glycoprotein (P-gp)
  - ABCB1 3435 C > T
  - The resultant amino acid (isoleucine) is unchanged from the reference DNA sequence
  - **Functional Effect:** ? Effect on P-gp function or expression
  - **Affected Drugs:** Efavirenz, cyclosporine

Non-Synonymous Codon SNP

- **Example:** Thiopurine methyltransferase (TPMT)
  - TPMT 615 G > A
    - Alanine changes to threonine
  - TPMT 874 A > G
    - Tyrosine changes to Cysteine
  - **Functional Effect:** ↓ TPMT enzyme activity
  - **Affected Drugs:** azathioprine, 6-mercaptopurine
  - May not be able to give the same dose to patients with this polymorphism

Premature Stop Codon SNP

- **Example:** CYP2C19*3
  - Nucleotide change G > A
  - The reference amino acid tryptophan is not coded
  - Results in termination of protein synthesis
  - **Functional effect:** CYP2C19*3 results in no enzyme activity
  - **Affected Drugs:** proton pump inhibitors (omeprazole, lansoprazole)

Gene Deletion

- **Example:** CYP2D6*5
  - Not a single nucleotide polymorphism
  - Thousands of nucleotide base pairs that comprise CYP2D6 gene are deleted
  - **Functional Effect:** loss of function for CYP2D6
  - **Poor metabolizer phenotype**
  - **Affected Drugs:** SSRIs, codeine, tamoxifen, β-blockers

Copy Number Variant

- **Example:** CYP2D6*XN
  - Extra copies of CYP2D6 gene are present
  - **Functional Effect:** Ultra rapid metabolizer (UM) phenotype
  - **Affected Drugs:** SSRIs, codeine, tamoxifen, β-blockers
Polymorphism Types Summary

- Single Nucleotide Polymorphism (SNP)
  - A single base substitution occurring within a gene
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  - May or may not alter protein synthesis
- Coding SNP
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  - Non-synonymous
  - Premature stop codon
- Other types of polymorphism (hundreds or thousands of nucleotides may be involved)
  - Gene deletion
  - Copy number variant

Patient Case

- 35 year old Asian female complains of dyspepsia & epigastric pain. Denies N/V and blood in stools. Urea breath test is positive. She is diagnosed with H. Pylori peptic ulcer disease
- PMH: No other significant PMH. NKDA
- Medications: Begins 10-day course of omeprazole, amoxicillin, & clarithromycin

Systematic Application of Pharmacogenomic Polymorphisms

- Identify the polymorphism and what it may affect
  - CYP2C19 enzyme
  - The variant CYP2C19*3 or *2 allele results in no activity

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>CYP2C19*1</th>
<th>CYP2C19*2</th>
<th>CYP2C19*3</th>
<th>CYP2C19*4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrates</td>
<td>Omeprazole</td>
<td>Omeprazole</td>
<td>Omeprazole</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Poor</td>
<td>intermediate</td>
<td>Ultrarapid</td>
<td>Ultrafast</td>
</tr>
</tbody>
</table>


Systematic Application of Pharmacogenomic Polymorphisms

- Identify the polymorphism and what it may affect
  - CYP2C19 enzyme
  - The variant CYP2C19*3 or *2 allele results in no activity

- Identify the individual affected
  - Rate of rapid metabolizers:
    - 56-81% in European and North Americans
    - 27-38% in Asian population
    - Increased activity of the enzyme
  - Rate of slow metabolizers:
    - 2.3-8.5% in Europeans
    - 8-23% in Chinese and Japanese population
    - Frequency of the CYP2C19*3 allele are higher in Asians
    - Decreased activity of the enzyme


Systematic Application of Pharmacogenomic Polymorphisms

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    - Frequency of the CYP2C19*3 allele are higher in Asians

- Relevance to a drug
  - Omeprazole plasma concentrations & exposure are higher in individuals with the CYP2C19*3 allele compared to those with CYP2C19*1 allele

Table 1 Incidence of the CYP2D6 enzyme phenotypes among different ethnic populations

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Caucasian, %</th>
<th>Ethiopian/ African, %</th>
<th>Asian, %</th>
<th>Hispanic, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolizer</td>
<td>2-10</td>
<td>1.8-8.1</td>
<td>6-12</td>
<td>2.3-6.6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
<td>N/A</td>
<td>1-2</td>
<td>0.9-1.7</td>
</tr>
<tr>
<td>Ultrarapid</td>
<td>0.8-4.3</td>
<td>0.9</td>
<td>1.7</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 3 Allele frequencies of CYP2C9 polymorphism

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>African-American, %</th>
<th>Black American, %</th>
<th>Asian, %</th>
<th>Caucasian, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9*2</td>
<td>2.9</td>
<td>0.4-3</td>
<td>0-1.3</td>
<td>8-19</td>
</tr>
<tr>
<td>CYP2C9*3</td>
<td>2.0</td>
<td>0.0-2.3</td>
<td>1.1-1.3</td>
<td>1-3-16</td>
</tr>
</tbody>
</table>


Table 4 Genotype and Omeprazole

<table>
<thead>
<tr>
<th>CYP2C19 Genotype</th>
<th>Omeprazole Exposure (mean + SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*1</td>
<td>368 ± 64</td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>1627 ± 532</td>
</tr>
<tr>
<td>CYP2C19*3</td>
<td>1530 ± 204</td>
</tr>
</tbody>
</table>

Futura et al. Clinical Pharmacology and Therapeutics 1999; 64(5):52-61
Systematic Application of Pharmacogenomic Polymorphisms

- Identify polymorphism and what it may affect
  - CYP2C19 enzyme
    - The variant CYP2C19*3 or *2 allele results in no activity
- Identify the individual affected
  - Rate of rapid metabolizers are
    - 56-81% in European and North Americans
    - 27-38% in Asian population
- Relevance to a drug
  - Omeprazole plasma concentrations & exposure are higher in individuals with the CYP2C19*3 allele compared to those with CYP2C19*1 allele
- Relevance to a disease
  - H. pylori cure rates vary based on CYP2C19 genotype in patients who are
    - on omeprazole-containing regimens
  - Patients with wild-type have decreased cure rate compared to patients with *3 or *2 variants of CYP2C19


Oncology 30%
Infectious Disease 19%
Psychiatry 17%
Cardiology 6%
Endocrinology 6%
Neurology 6%
Gastroenterology 6%

Figure 1. Percentage of FDA-approved medications in each therapeutic area. Percentages may differ from categories given, based on data sources and operational definitions.

Cheek, DJ, et al. Journal of Nursing Scholarship, 2015; 47:6, 496-504

Table 1

<table>
<thead>
<tr>
<th>Therapeutic Area: Oncology</th>
</tr>
</thead>
</table>

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
Accessed November 27, 2017
Therapeutic Area: Psychiatry

- Primarily affected by Phase I enzymes: CYP2D6 and CYP2C19
  - CYP2D6: 80% and CYP2C19: < 10%
- Trisetic antidepressants:
  - The guidelines recommend a 50% dose reduction of amitriptyline and nortriptyline in persons who are CYP2D6 or CYP2C19 slow metabolizers.
  - For CYP2D6 ultrarapid metabolizers (UMs), therapy with amitriptyline or nortriptyline should be avoided, or the initial target dose should be increased.
- SSSs: FDA label for citalopram recommends a maximum dose of 20 mg/day in lsson PMs.
- Testing is not routine since it has a wide therapeutic window
- HLA-B*1502 for carbamazepine and phenytoin.
- Increased risk for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TENs)
- FDA and The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommend testing in Asian population.
- 10–15% in patients from China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan
- 2–6% in patients from South Asia and India
- <0.01% in patients of European, Hispanic, Native American, and African descent

- Article provides excellent tables with recommendations for dose adjustment for different genetic variants and pharmacogenomic testing resources for variants influencing neuropsychiatric medications.

Therapeutic Area: Anticoagulation (warfarin)

- Metabolism affected by CYP2C9 and VKORC1
  - CYP2C9*2 and *3 variant + VKORC1 activity by 50-90% = Higher warfarin concentration
    - Caucasians: 1-20%; Asians & African-Americans: < 4%
  - VKORC1 (vit K epoxide reductase complex subunit 1)
    - VKORC1 1173G > T (Asians: 82-85%; Caucasians: 14-41%, African-Americans: 9%)
    - 5 common haplotypes categorized into Group A and B
      - Group A (1 and 2) – require lower warfarin dose (Asians: 89%; Caucasians: 37%; AA: 14%)
      - Group B (7,8,9) – require higher warfarin dose (Asians: 10%, Caucasians: 58%; AA: 49%)
    - Genotype BB: Caucasians 18% - require higher warfarin dose
  - Clinical algorithm for warfarin dosing
    - http://www.warfarinidosing.org

Warfarin: package insert

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1+/1+</td>
<td>*1+/1+</td>
</tr>
<tr>
<td>*1+/1+</td>
<td>*1+/1+</td>
</tr>
<tr>
<td>*1+/1+</td>
<td>*1+/1+</td>
</tr>
</tbody>
</table>

Question 2

Which polymorphism will most likely influence warfarin dosing?
A. CYP2C9 and VKORC1
B. CYP2C19 and VKORC1
C. CYP2D6 and VKORC9
D. CYP2D6 and VKORC1
FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

- **Non-Relevant Genotypes:** some labels have a gene biomarker listed in the FDA table; detail shows that the gene is NOT relevant for that drug
  - Example: citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.
  - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.
  - Example: prasugrel has four entries – CYP2C19, CYP2C9, CYP3A5, CYP2B6. The “Use in Specific Populations” section in the Effient (prasugrel) insert says:
    - There was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

- **Drug Interactions:** some labels include pharmacogenetic information that apply to drug interactions rather than the primary metabolism of the given drug.
  - Example: escitalopram CYP2D6 Poor Metabolizers. The escitalopram “Drug Interactions” section mentions the following with regard to an escitalopram – CYP2D6 interaction:
    - In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers. There are...data suggesting a modest CYP2D6 inhibitory effect for escitalopram...caution is indicated in the co-administration of escitalopram and drugs metabolized by CYP2D6.

Factors to Consider with Pharmacogenomics Testing

- Legal issues
- Cost implications
- Social issues
Challenges of Pharmacogenomics Implementation

- Education of health care providers
- Access
  - Availability of test
  - Insurance coverage
- Feasibility
  - Turn around time
  - Efficiency
- Cost
  - Counseling
  - Genetic test

Where to find more information on Pharmacogenomics

- National Institute of Health – National Human Genome Research Institute
  www.genome.gov
- US Food and Drug Administration
- Clinical Pharmacogenetics Implementation Consortium (CPIC®)
  https://cpicpgx.org/
- PharmGKB - NIH-funded resource that provides information about how human genetic variation affects response to medications
  www.Pharmgkb.org

Pharmacogenomic Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test</th>
<th>Self-Pay Cost ($)</th>
<th>Contract Cost</th>
<th>Specimen</th>
<th>Results in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Amplichip CYP450</td>
<td>750-1,400</td>
<td>1,225</td>
<td>Whole blood</td>
<td>8-10</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>CYP2D6</td>
<td>589</td>
<td>490</td>
<td>Whole blood Buccal swab</td>
<td>5</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2/CEP 17 FISH</td>
<td>333</td>
<td>277</td>
<td>Formalin–fixed, paraffin–embedded tumor tissue</td>
<td>3-7</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1</td>
<td>441</td>
<td>368</td>
<td>Buccal swab</td>
<td>5-7</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9 and VKORC1</td>
<td>517</td>
<td>517</td>
<td>Whole blood Buccal swab</td>
<td>10</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA-B*57:01</td>
<td>157</td>
<td>157</td>
<td>Whole blood Buccal swab</td>
<td>5</td>
</tr>
</tbody>
</table>

PharmGenEdTM team personal communication with selected labs. Jan-Feb 2009

Question #3
Which of the following resources is useful for finding how a genetic variation affects response to a specific medication?

A. National Institute of Health – National Human Genome Research Institute
B. PharmGKB
C. FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
D. B and C

Genetic tests


Question #4

A patient’s pharmacogenetic laboratory test report shows that he is a CYP2D6 poor metabolizer. He is prescribed Tylenol with codeine for an ankle sprain.

What is the effect of CYP2D6 poor metabolizer phenotype with codeine?

A. Patient may experience increased side effect
B. Patient may experience decreased efficacy
C. Patient may have increased exposure to the metabolite
D. A and C
Take home points

• Pharmacogenomics is the study of how genetic makeup affects clinical outcomes of drug therapies.
• Currently, there are only a number of medications that require genotype testing prior to initiation of therapy. However, additional clinical applications may be around the corner.
• Identification of opportunities to perform genetic testing and application of results is key.
• Genetic testing is readily available but costly among other barriers.