Pharmacogenomics 101: Precision Medicine for Older Adults

Stephanie Sibicky, PharmD, MEd, BCGP, BCPS, FASCP
Associate Clinical Professor
Northeastern University School of Pharmacy and Pharmaceutical Sciences
@stephsibicky

Meet the Speaker:
Stephanie L. Sibicky, PharmD, MEd, BCGP, BCPS, FASCP

- Associate Clinical Professor, Northeastern University School of Pharmacy and Pharmaceutical Sciences, Boston, MA
- Clinical Pharmacy Faculty in Internal Medicine at Brigham and Women’s Hospital, Boston, MA
Disclosure

I have no relevant financial relationships with commercial interest pertaining to the content of this presentation.

Learning Objectives

• Define nomenclature related to precision medicine and pharmacogenomics.
• Discuss economic, social, and ethical considerations pertaining to pharmacogenomic testing.
• Recommend pharmacogenomic testing, when applicable, in the care of older adults.
• Interpret the results of pharmacogenomic testing to assist with medication selection and dosing.
• Utilize evidence-based guidelines and literature to develop a patient-specific recommendation based on pharmacogenomic testing.
Precision Medicine & Pharmacogenomics

- **Precision medicine** or “personalized medicine” is an innovative approach to tailoring disease prevention and treatment that considers differences in people’s genes, environments, and lifestyles.

- **Pharmacogenetics** is the study of the relationship between individual gene variants and variable drug effects.

- **Pharmacogenomics (PGx)** is defined as the study of the relationship between variants in a large collection of genes, up to the whole genome, and variable drug effects.

### Genetic Nomenclature

- DNA is transcribed to RNA to make proteins from a three-nucleotide codon.

- Genes are a series of codons that create a protein:
  - Exon = codes for an amino acid
  - Intron = non-coding region
  - Regulatory regions = control transcription

- Phenotype is the outward expression of a gene.
Alleles

- Alleles are the specific spot on a chromosome where the sequence of nucleic acid bases exist
- Humans have two copies of each chromosome, two alleles for each position of DNA
- Allele types:
  - Wild-type – most common type or reference allele (usually *1)
  - Variant – polymorphic or minor allele (indicated by *#)
- Genotype refers to the combination of alleles you have
  - Two identical alleles – homozygous
  - Two different alleles – heterozygous

Genetic Variation

- Variant is a difference in a sequence compared to the reference
  - Common variant (> 1% of population) = polymorphism
  - Rare variant (< 1% of population) = mutation
- Single-nucleotide polymorphisms (SNPs) are single nucleotide variants, where one nucleotide replaces another (e.g., A to G)
  - Synonymous SNP = no change in protein coded
  - Nonsynonymous SNP = different protein coded
Drug-Metabolism Polymorphisms

- **Phase I (CYP450 enzymes)**
  - 57 different isoenzymes in humans
  - Most notable CYP2A6, 2B6, 2C9, 2C19, 2D6, and 3A4/5

- **Phase II (NAT, UGT, glutathione S-transferase)**
  - Thiopurine S-methyltransferase (TPMT)
    - Four mutations affecting inactivation of 6-mercaptopurine (metabolite of azathioprine)
    - Homozygous and heterozygous alleles of TPMT*3A, *2, *3B, *3C at increased risk of hematological toxicities

Examples of FDA-Labeling with PGx Information: Drug Metabolism Polymorphisms

- **CYP2D6**
  - Codeine
  - Thioridazine
  - Fluoxetine
  - Tramadol
  - Carvedilol

- **CYP2C19**
  - Clopidogrel
  - Citalopram
  - Pantoprazole
  - Voriconazole

- **CYP2C9**
  - Warfarin
  - Rifaxin
  - Celecoxib
  - Isoniazid

- **NAT**
  - Rifampin
  - Isoniazid
  - nilotinib

- **UGT**
  - Irinotecan
  - Nilotinib
  - 6-mercaptopurine

- **TPMT**
  - Azathioprine

Let’s Look at an Example: CYP2D6

- Highly polymorphic and responsible for up to 25% of medication metabolism
- Medications that are a 2D6 substrates include many antidepressants (e.g., SSRIs, TCAs), antipsychotics (e.g., haloperidol), opioids, β-blockers (e.g., metoprolol, carvedilol)

<table>
<thead>
<tr>
<th>Normal function</th>
<th>CYP2D6<em>1, CYP2D6</em>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased function</td>
<td>CYP2D6<em>9, CYP2D6</em>10, CYP2D6<em>17, CYP2D6</em>41</td>
</tr>
<tr>
<td>No function</td>
<td>CYP2D6<em>3, CYP2D6</em>4, CYP2D6<em>5, CYP2D6</em>6</td>
</tr>
</tbody>
</table>

CYP2D6 Phenotypes

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (UM)</td>
<td>About 1-2% of patients</td>
<td>(*1/*1)xN, (*1/*2)xN, (*2/*2)xN</td>
</tr>
<tr>
<td>Normal metabolizer (NM)</td>
<td>About 77-92% of patients</td>
<td>*1/*1, *1/*2, *1/*9, *1/*41, *2/*2</td>
</tr>
<tr>
<td>Normal/intermediate metabolizer</td>
<td>Two decreased function alleles or one normal + one decreased function allele</td>
<td>*1/*4, *1/*5, *41/*41</td>
</tr>
<tr>
<td>Intermediate metabolizer (IM)</td>
<td>About 2-11% of patients</td>
<td>*4/*10, *4/*41, *5/*9</td>
</tr>
<tr>
<td>Poor metabolizer (PM)</td>
<td>About 5-10% of patients</td>
<td>*3/*4, *4/*4, *5/*5, *5/*6</td>
</tr>
</tbody>
</table>

xN – number of gene copies

Variant CYP2D6 Effects on Drug Metabolism

If PM, cannot convert tramadol to active metabolite = little to no analgesic effect

If UM, converts tramadol to active metabolite = enhanced efficacy and risk for toxicity

Drug Transporter Polymorphisms

• Proteins that facilitate drug transport across GI tract, excretion into bile/urine, distribution across blood brain barrier, uptake into cells

• Types:
  • ATP-binding cassette transporters (e.g., p-glycoprotein – ABCB1 gene)
  • Solute carrier transporters (e.g., OATP1B1 – SLCO1B1 gene)

• Example: **simvastatin**
  • OATP1B1 on hepatocytes to help with liver uptake of statins
  • Polymorphic variants with decreased function of SLCO1B1 include *5, *15, *17
  • Decreased function leads to more simvastatin available in the plasma and increased risk for myopathy and adverse effects
Drug Target Polymorphisms

- Receptors, enzymes, ion channels, signaling pathways, adverse event predisposition
- Can compound pharmacokinetic properties (e.g., drug transporters, enzymes)
- Example: warfarin
  - CYP2C9 metabolism of S-warfarin + VKOR inhibition
  - Variants in VKORC1 gene result in variable VKOR expression and warfarin sensitivity
  - May impact dosing of warfarin

Warfarin Product Labeling

**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/*2</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>*1/*3</th>
<th>*2/*2</th>
<th>*2/*3</th>
<th>*3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>5-7 mg</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
<td>0.5-2 mg</td>
<td>0.5-2 mg</td>
</tr>
</tbody>
</table>

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.
Audience Response Question #1

PH is a 78-year-old woman who was diagnosed with atrial fibrillation after a syncopal fall. She is at high risk of bleeding and it is decided to start warfarin because she can be closely monitored. PH informs you that she had pharmacogenomics testing performed and gives you the results indicating her CYP2C9 is *3/*3.

Which dose of warfarin should we start for PH?

A. 1 mg  
B. 3 mg  
C. 5 mg  
D. 7 mg

Warfarin Product Labeling

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></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.
Considerations for Older Adults

- Exposed to more medications, multimorbidity, age-related changes
- Adverse drug events (ADEs) account for large proportion of hospitalizations for older adults
- Genetic testing may assist in the prevention of adverse outcomes
  - May reduce re-hospitalization at 60 days in patients > 50 years old taking ≥ 6 medications
  - PGx testing in ≥ 65 years old reduced hospitalization rates by 39%, emergency department visits by 71%, saving $218 per patient over 4 months
- Examples:
  - “Start low and go slow” – what if the patient is an ultra-rapid metabolizer?
  - What if small doses of a medication are causing disproportional ADEs?

Economic, Social, Ethical Considerations

**Economic**
- Testing can be costly if not reimbursable from insurance
- Increasing trend in insurance coverage over the years
- Assistance programs may be available from laboratories

**Social and Ethical**
- Shared-decision making process
- Willingness of patient to participate (informed consent)
- Privacy and ownership of genetic data
- Fear of employer and/or insurance discrimination
- Difference between genetic testing and medication-specific testing

Pharmacogenomic Testing

- **Collection via blood sample, saliva, cheek swab**
- **Can be for single gene-drug pair test or whole genome**
- **Consider turnaround time if in-house lab or send out**
- **Before prescribing (preemptive), after prescribing (reactive), point-of-care**
- **Price ranges from $200-500, may be reimbursable if FDA-required for medication**
- **Importance of communication of results through electronic medical record or to each provider manually**

Patient and Caregiver Education

**Before the test:**
- The role of genes in drug response
- Purpose of acquiring the test
- What are the risks and benefits?
- Are there therapy limitations or alternatives?
- How PGx testing could help in the future

**After receiving test results:**
- What did the results tell you?
- What changes need to be made to medications?
- The impact of these results for future prescribing
- Communication of results to all providers
Helpful Resources

Pharmacogenomics Knowledge Base (PharmGKB)
http://www.pharmgkb.com

Clinical Pharmacogenetics Implementation Consortium (CPIC)
http://cpicpgx.org

US FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

Dutch Pharmacogenetics Working Group (DPWG)
http://www.pharmgkb.org/page/dpwg

Pharmacogene variation
http://www.pharmvar.org

Professional organizations for drug-gene pairs

---

Case RT

RT is a 72-year-old man who has failed several medications for major depressive disorder. He has tried citalopram with no effect and paroxetine and venlafaxine produced intolerable side effects. You are consulted about potentially performing pharmacogenomic testing for this patient and are asked for alternatives by RT’s psychiatry team.

How would you respond to this question?
Antidepressants and PGx: The Evidence

Utility of Integrated Pharmacogenomic Testing to Support the Treatment of Major Depressive Disorder in a Psychiatric Outpatient Setting

| Population                                      | 227 patients, age 18-72 diagnosed with MDD based on DSM-IV  
|                                                | Minimum score of 14/17 on Hamilton Rating Scale for Depression (HAMD-17) |
| Intervention and Comparison                     | Guided by pharmacogenomics testing (n=114)  
|                                                | Unguided (n=113) |

Outcome

At baseline, weeks 2, 4, and 8 patients completed the HAMD-17, Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C16), and Patient Health Questionnaire (PHQ-9) via telephone

Results

- Greater percentage improvement in symptoms from baseline for guided v. unguided HAMD-17 (46.9% v. 29.9%, P<0.0001), QIDS-C16 (44.8% v. 26.4%, P<0.0001), and PHQ-9 (40.1% v. 19.5%, P<0.001)
- Greater remission rates at 8 weeks guided v. unguided HAMD-17 (30.6% v. 21.5%, P=0.19), QIDS-C16 (26.4% v. 12.8%, P=0.028), and PHQ-9 (25.4% v. 16.1%, P=0.14)
Antidepressants and PGx: More Evidence

### Efficacy of Prospective Pharmacogenomic Testing in the Treatment of Major Depressive Disorder: Results of a Randomized, Double-blind Clinical Trial

| Population | • Multi-center study in Spain, 527 patients, mean age 51.2±12.6, diagnosed with MDD based on DSM-IV  
|            | • Minimum score of 4 on Clinical Global Impression-Severity (CGI-S) scale |
| Intervention and Comparison | • Guided by pharmacogenomics testing (n=155)  
|                             | • Control group (n=161) |

### Outcome

Efficacy of pharmacogenetic information looking at proportion of patients achieving a sustained response through 12-week follow-up using the Patient Global Impression of Improvement (PGI-I) score

### Results

Response rate based on subjects reporting a PGI-I score ≤ 2 in study group (guided) v. control group (unguided), 51.8% v. 31 %, P<0.01

Case RT: Continued

RT is a 72-year-old man who has failed several medications for major depressive disorder. He has tried citalopram with no effect and paroxetine and venlafaxine produced intolerable side effects. You are consulted about potentially performing pharmacogenomic testing for this patient and are asked for alternatives by RT’s psychiatry team.

Since you know there is added benefit for using PGx-guided therapy, you obtain consent and order the test for this patient, focusing on the polymorphisms concerning for antidepressants.

Where can you find which tests you should conduct?

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients’ genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC’s guidelines, processes and projects have been endorsed by several professional societies - read more.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines contain more details on minimizing and managing conflicts of interest.

View CPIC's process for prioritizing CPIC guidelines

Search: antidepressants

<table>
<thead>
<tr>
<th>GENES</th>
<th>CYP2D6 CYP3A4 CYP4F2</th>
<th>amitriptyline clomipramine desipramine doxepin imipramine nortriptyline trimipramine</th>
</tr>
</thead>
</table>

https://cpicpgx.org/guidelines/
# Predicted Phenotypes (CPIC Guidelines)

<table>
<thead>
<tr>
<th>Likely Phenotype (% of patients)</th>
<th>Genotype</th>
<th>Example Diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (1-2)</td>
<td>Duplicate, functional</td>
<td>*1/*1xN, *1/*2xN, *2/*2xN</td>
</tr>
<tr>
<td>Extensive metabolizer (EM, 77-92)</td>
<td>2 normal, 2 decreased, 1 normal + 1 no function, 1 normal + 1 decreased</td>
<td>*1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2, *41/*41</td>
</tr>
<tr>
<td>Intermediate metabolizer (2-11)</td>
<td>1 decreased + 1 no function</td>
<td>*4/*10, *4/*41, *5/*9</td>
</tr>
<tr>
<td>Poor metabolizer (5-10)</td>
<td>Only no function</td>
<td>*3/*4, *4/*4, *5/*5, *5/*6</td>
</tr>
<tr>
<td>Ultrarapid metabolizer (5-30)</td>
<td>2 increased function or 1 normal + 1 increased function</td>
<td>*17/*17, *1/*17</td>
</tr>
<tr>
<td>Extensive metabolizer (EM, 35-50)</td>
<td>2 normal function</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizer (18-45)</td>
<td>1 normal or 1 increased + 1 no function</td>
<td>*1/*2, *1/*3, *2/*17</td>
</tr>
<tr>
<td>Poor metabolizer (2-15)</td>
<td>2 no function</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
</tbody>
</table>

---

## Case RT: Test Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>*1F/*1F</td>
<td>Rapid metabolizer</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>*1/*1</td>
<td>Normal</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*18</td>
<td>Intermediate</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*17</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*3/*4</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>Normal</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*3/*3</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

What is RT’s phenotype?
Case RT: Test Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>*1F/*1F</td>
<td>Rapid metabolizer</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>*1/*1</td>
<td>Normal</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*18</td>
<td>Intermediate</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*17</td>
<td>Ultrarapid metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*3/*4</td>
<td>Poor metabolizer</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>Normal</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*3/*3</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

Interpreting RT’s Results

- CYP2C19 *1/*17 Ultrarapid metabolizer
- CYP2D6 *3/*4 Poor metabolizer

- Does it make sense that RT was a non-responder to citalopram?

- Does it make sense that RT had intolerable side effects with paroxetine and venlafaxine?
Interpreting RT’s Results

<table>
<thead>
<tr>
<th>CYP2C19</th>
<th>*1/*17</th>
<th>Ultrarapid metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>*3/*4</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

- Does it make sense that RT was a non-responder to citalopram?
  - Citalopram is metabolized by CYP2C19
  - Likely metabolized before effect could be seen

- Does it make sense that RT had intolerable side effects with paroxetine and venlafaxine?
  - Paroxetine and venlafaxine are metabolized by CYP2D6
  - Likely more exposure to active medication in blood stream
“Traffic Light” Approach

Use as directed
- Desvenlafaxine
- Levomilnacipran

Use with caution
- Bupropion
- Selegiline
- Sertraline
- Trazodone
- Vilazodone

Use with increased caution and more frequent monitoring
- Amitriptyline
- Citalopram
- Clomipramine
- Desipramine
- Dibenzepine
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Imipramine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Venlafaxine
- Vortioxetine

Desvenlafaxine and levomilnacipran are not covered on RT’s insurance and the team would like to start sertraline. How would you respond?

Back to the CPIC Guidelines...

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implication</th>
<th>Therapeutic Recommendation</th>
<th>Classification of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased metabolism when compared to extensive metabolizers.</td>
<td>Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by 2C19.</td>
<td>Optional</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal metabolism.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced metabolism when compared to extensive metabolizers.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by 2C19.</td>
<td>Optional</td>
</tr>
</tbody>
</table>

Take Home Points

• It is important for all members of the interdisciplinary team to have a general understanding of the terminology used when employing personalized medicine

• Pharmacists have extensive knowledge in pharmacokinetics and pharmacodynamics which makes us well suited for this role

• Resources available can help team members make holistic patient care decisions about precision medicine and pharmacogenomic testing considering social, economic, and ethical factors

• Data is still emerging about the use of pharmacogenomics in practice

Questions?

Stephanie Sibicky, PharmD, MEd, BCGP, BCPS, FASCP
s.sibicky@northeastern.edu
@stephsibicky
References


Abbreviations from Slide 14

- ATP – adenosine triphosphate
- ABCB1 – ATP-binding cassette subfamily B member 1
- OATP1B1 – organic anion transport proteins 1B1
- SLCO1B1 – solute carrier organic anion transporter family member 1B1