APPLYING GENETIC TESTING AND PHARMACOGENOMICs IN PRACTICE

Robbie Kidd, PharmD, PhD
Professor and Chair
Department of Biopharmaceutical Sciences
Bernard J. Dunn School of Pharmacy
Shenandoah University

Objectives

- Identify recent pharmacogenomic updates to selected products’ full prescribing information
- Recognize patient scenarios when pharmacogenomic testing could provide clinically actionable information
- Analyze the results of pharmacogenomic testing
- Discuss appropriate sources for pharmacogenomic guidelines
- Apply the pharmacogenomic test results to a patient scenario

Disclosure Statement

I do not have any financial relationships to disclose

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

President Obama - January 30, 2015

2.2+ MILLION non-error, serious ADEs

106,000+ deaths

$136-177 BILLION cost to treat

50% due to genetic factors

Causes of Death: 2014

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heart disease</td>
<td>614,348</td>
</tr>
<tr>
<td>2</td>
<td>Cancer</td>
<td>591,699</td>
</tr>
<tr>
<td>3</td>
<td>Lower respiratory disease</td>
<td>147,101</td>
</tr>
<tr>
<td>4</td>
<td>Accidents</td>
<td>136,053</td>
</tr>
<tr>
<td>5</td>
<td>Cerebrovascular disease</td>
<td>333,103</td>
</tr>
<tr>
<td>6</td>
<td>non-error ADEs</td>
<td>106,000+</td>
</tr>
<tr>
<td>7</td>
<td>Alzheimer’s disease</td>
<td>93,541</td>
</tr>
<tr>
<td>8</td>
<td>Diabetes</td>
<td>76,488</td>
</tr>
<tr>
<td>9</td>
<td>Influenza and pneumonia</td>
<td>55,227</td>
</tr>
<tr>
<td>10</td>
<td>Kidney disease</td>
<td>48,146</td>
</tr>
</tbody>
</table>

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- Currently, 165 drugs with pharmacogenomic label content
- Almost one-half of these are metabolized by CYP2D6, CYP2C19 or CYP2C9
- Eight pharmacogenomic markers are included in Boxed Warning

Clinical Pharmacogenomics

- The goal of clinical pharmacogenomics is to get the right drug at the right dose to the right patient.
  - Utilize established associations between genetic variations and response or toxicity to a particular medication (e.g., CYP2C19 drug metabolism)
  - Utilize established associations between genetic variations and disease to select the best medication for treatment (HER2 expression and chemotherapy selection)

Select CYP2D6 Alleles

<table>
<thead>
<tr>
<th>Allele</th>
<th>Change</th>
<th>Consequence</th>
<th>Caucasians</th>
<th>African-Americans</th>
<th>Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*1</td>
<td>frameshift</td>
<td>nonfunctional</td>
<td>1-2</td>
<td>-</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>defective splicing</td>
<td>nonfunctional</td>
<td>20</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>gene deletion</td>
<td>nonfunctional</td>
<td>4</td>
<td>6</td>
<td>4-6</td>
</tr>
<tr>
<td>CYP2D6*6</td>
<td>frameshift</td>
<td>nonfunctional</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>Pro35Ser</td>
<td>decreased</td>
<td>&lt;2</td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>Thr107Ile</td>
<td>decreased</td>
<td>&lt;1</td>
<td>22</td>
<td>-</td>
</tr>
</tbody>
</table>

General PGx Guidelines

<table>
<thead>
<tr>
<th>Phenotype*</th>
<th>General Genotype</th>
<th>Specific Genotype Example</th>
<th>Average Dosea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal metabolizer (NM)</td>
<td>wild-type/wild-type</td>
<td>*1/*1</td>
<td>normal</td>
</tr>
<tr>
<td>Intermediate metabolizer (IM)</td>
<td>wild-type/variant</td>
<td>*1/*4</td>
<td>Reduce by 1/3</td>
</tr>
<tr>
<td>Poor metabolizer (PM)</td>
<td>variant/variant</td>
<td>*4/*4</td>
<td>Reduce by 2/3 (consider alternative)</td>
</tr>
<tr>
<td>Rapid or Ultra-rapid metabolizer</td>
<td>wild-type x 3+</td>
<td>*4/*4N</td>
<td>Increase by 2/3</td>
</tr>
</tbody>
</table>

*Phenotype is not rigidly determined by genotype; it is also influenced by other factors (e.g., pathophysiology, drug-drug interactions, drug-food interaction, etc.)

a Assumes active parent compound, not active metabolite(s)
Case 58 yo man with supraventricular tachycardia associated with angina underwent coronary angiographic assessment. It revealed mild coronary artery disease in his left main coronary artery and significant stenosis of the ramus medianus (left intermediate artery). A drug-eluting stent was deployed and treatment with clopidogrel initiated. He was genotyped for CYP2C19 and the results are as follows: CYP2C19*1*3.

**Pop quiz**
Since the patient's genotype is CYP2C9*1*3, their CYP2C9 drug metabolizing phenotype is:

a. extensive metabolizer
b. intermediate metabolizer
c. poor metabolizer
Clopidogrel
Oct. 2009

Pharmacogenetics

<table>
<thead>
<tr>
<th>CYP2C19 Phenotype and Genotype Frequency</th>
</tr>
</thead>
</table>
| The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post-hoc clinical trial analyses (substudies of CLARITY-TIMI 28 \(^{[#405]}\) and TRITON-TIMI 38 \(^{[#1,477]}\)) and 5 cohort studies \(^{[#6,489]}\). In CLARITY-TIMI 28 and one of the cohort studies \(^{[#765]}\), ticagrelor cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies \(^{[#5,358]}\), ticagrelor patients with at least one CYP2C19 variant allele (intermediate and poor metabolizers) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) compared to extensive metabolizers. In the fifth cohort study \(^{[#2,208]}\) (Siansu), the increased event rate was observed only in poor metabolizers.

Population
Risks

- 25-30% have one CYP2C19 variant allele
- 2-4% have two CYP2C19 variant alleles
- Patients with one or more CYP2C19 variant allele
  - 32% decrease in exposure to active metabolite
  - 53% increase in risk of death (CV cause)
  - 3 fold increase in risk of stent thrombosis
- Prasugrel vs clopidogrel therapy results in RR of 0.57 (95% CI of 0.39-0.83) of CV death, MI, or stroke

Pop quiz

Since the patient is CYP2C19 intermediate metabolizer, his clopidogrel dose should be a:
- normal dose
- reduced dose
- increased dose
- alternative therapy

Clopidogrel Case

58 yo man with supraventricular tachycardia associated with angina underwent coronary angiographic assessment. It revealed mild coronary artery disease in his left main coronary artery and significant stenosis of the ramus medianus (left intermediate artery). A drug-eluting stent was deployed and treatment with clopidogrel initiated.

He is a CYP2C19*1*3 intermediate metabolizer

So what do we do...

Background

One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines. CPIC provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs. The guidelines can center on genes (e.g. thiorurine methyltransferase and its implications for thiorurines) or around drugs (e.g. warfarin and CYP2C9 and VKORC1). Priority is given to genotyping tests that are already offered in CLIA-approved clinical settings.
Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Cogabaplatin Therapy: 2013 Update


ATCTTAACAAGAAGAGAAGGCTTCAATGGATTCTCTTGTGGTCCTTG TGCTCTGTCTC TCATGT TTGC TTCTCCTTTC ACTCTGGAG ACAG AGCTCTGGGAG AGGAAAACTCCCTCCTGGCCCCAC TCCTCTCCC AGTGATTGGAAATATCC TAC AGATAGGTATTAAGG ATC AGCAAATCC TTAACCAATG TAAGTATGCTCCTT

CAGTGGCTTGCAAAAGGTAAGTAAATTCACCTG TATTTTTTAAATAAAGTGTATCCCTAGAGGTACATGTTACAAGAGGTAATGGTAAAGTAAAATACTTTGAAAGGCTTTTG TTGCCTTTTCCAG TC TGTC AGTGTCAAATAG TGGAATGAAACC ATGTATTTTGTG AGTAGAGAAAG ATTTGGGTCTTTG CATG TTAGATTCAA AATAACAAGTGTCAATAGTTTGAAAAGCTGTGTTCCTTC TTCATTTC ATAACC ATTTGCTATAA TTTTTTGGCTGAAGGTAAATGGTAAGGTATTGTGGGATCTGGTC AGCAGCCCAC AAAGCAACTGG GCTCTCTC TTTTTTCCC AGGTGGATCGGC AGGTTGAG AAATAATAG ACAC ACAAGATAGTG AAA GCTGGGTCCAGGG GGGTCACCGCCTTCTGGTCCCATGGTGCCAAGAATGCACTGGATATACCAGC ATTTATTATTAA GTTTAG TGAGGGCAGGGGTAGGTTAG TGAGGGATTTAGGGTCATTTG ATTATG AGGTGAGATGG TCAC ATGGGGATGAAG TAATTC TTTAACATAAC ATTTGTATGTAGAAGTACAGTACATTTGTAT TAG-AGTACAG T

Warfarin - update 2007

Table 5: Relationship Between S-Warfarin Clearance and CYP2C9 Genotype in Caucasian Patients

<table>
<thead>
<tr>
<th>CYP2C9 Genotype</th>
<th>N</th>
<th>S-Warfarin Clearance/Lean Body Weight (ml/min/m²) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>118</td>
<td>0.901 (0.252)</td>
</tr>
<tr>
<td>*1/*2 or *1/*3</td>
<td>59</td>
<td>0.941 (0.221)</td>
</tr>
<tr>
<td>*2/*3 or *3/*3</td>
<td>11</td>
<td>1.023 (0.211)</td>
</tr>
<tr>
<td>Total</td>
<td>188</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Standard deviation are given. Patient comparisons indicated significant differences among all genotypes.

Warfarin reduces the expression of vitamin K from vitamin K epoxide in the vitamin K cycle. Through inhibition of vitamin K reductase (VKOR), a multifunctional enzyme complex. Carcinogenic nucleic acid polymorphisms in the VKORC1 gene (previously the -1636A-G allele) have been associated with lower dose requirements for warfarin. In 201 Caucasian patients treated with anticoagulation dose, genotypic variations in the VKORC1 gene were associated with lower anticoagulant doses. In this study, about 80% of the variance in anticoagulant dose could be attributed to variations in the VKORC1 gene alone. About 50% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, weight, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients. Similar observations have been reported in Asian patients.

Warfarin - update 2010

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1 Genotypes</th>
<th>CYP2C9 Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Caucasian male had two teeth extracted. But….

Also has severe nausea and occasional vomiting.

Now complains of no pain relief.
Codeine Case

- A Caucasian male had two teeth extracted and was given a prescription for acetaminophen with codeine
- Now complains of no pain relief
- Also has severe nausea and occasional vomiting
- Genotyping revealed the patient is CYP2D6*2*2...

Pop quiz

Since the patient’s genotype is CYP2D6*2*2, their CYP2D6 drug metabolizing phenotype is:

a. extensive metabolizer
b. intermediate metabolizer
c. poor metabolizer

Phenytoin Case

- 64 year old female, African-American who was placed on oral phenytoin 100 mg TID after a 5 day hospital stay for status epilepticus.
- Thirteen days after discharge from the hospital she presented to the ED with complaints of slurred speech, mental confusion, memory loss and not being able to stand. These symptoms had progressively worsened over the previous week.
- Phenytoin serum concentration 49.5 mcg/mL

Traditional Assessment

✓ Screened for taking it correctly
✓ Screened for drug-drug interactions
✓ Screened for liver dysfunction

No easily, identifiable cause of the grossly elevated phenytoin serum concentration.
Pharmacogenomics Tests

- Just another lab test to assist in therapeutic decision making
- Wide applicability since it will effect drugs that are primarily dependent on metabolism for their elimination
- The key is how to interpret and use the information to personalize therapy
- Currently, CPIC has information on 211 drugs

When will we break through?