Personalized Prescribing: Using Genetic Testing to Guide Drug and Dose Selection

Lindsay S. Elliott, Pharm.D., CGP
Disclosure

• I, Lindsay Elliott, am a pharmacy consultant for Genelex Corporation in conducting a clinical trial in which their lab performs testing and I use YouScript® Personalized Prescribing System to make therapy recommendations.
Overview

- Characteristics of CYP450 enzymes
- Drugs subject to significant interactions
- MRPs in patient cases
- DNA testing companies
ADVERSE DRUG EVENTS
CYP450s & DRUGS
ADEs: Avoidable major medical problem

2.2 MILLION severe adverse drug reactions per year

FOURTH leading cause of death in the U.S.

100,000 deaths per year by properly prescribed drugs

80,000 deaths per year by improperly prescribed drugs

COST LEADER for malpractice payouts

Sources: US Centers for Disease Control and Prevention, US Food and Drug Administration, Journal of the American Medical Association and others
Drug-drug interactions (DDIs) are a major cause of adverse outcomes, with up to 37% of DDI-related ADRs necessitating a hospital admission\(^4\), however, drug-gene interactions may be just as serious. The FDA Pharmacogenomic Guidance for the drug development industry states that ‘difference in drug exposures between extensive metabolizer (EM) and poor metabolizer subgroups would generally represent the most extreme change that could be caused by a strong inhibitor or pathway.’\(^5\)

Thus, if a poor metabolizer represents the most extreme inhibitor, the patient may be at a major risk if given a medication that goes through that pathway. Drug-gene interactions should be considered to be similar in scope to drug-drug interactions.”

With genetics

Without genetics

Advertised dose

Personalized dose
PHARMACOKINETIC BIOMARKERS
“What the body does to the drug”
Somatic vs. Germline

- **Somatic**
  - Acquired (by cancer cells)
  - Usually associated with efficacy
  - Examples: ABL1, ALK, BRAF, EGFR, HER2, KRAS, KIT

- **Germline**
  - Inherited
  - Examples: CYP2D6, CYP2C9, CYP3A4, CYP2B6, DPYD, SLCO1B1, TPMT, UGT1A1
Cytochrome P450s Metabolize Drugs

**Major enzymes**
- CYP2D6
- CYP2C9
- CYP2C19
- CYP3A4
- CYP3A5
- CYP2B6
- CYP1A2
- CYP2A6
- CYP2C8
- CYP2E1
Most common meds are metabolized by these CYP450s

<table>
<thead>
<tr>
<th></th>
<th>CYP2D6</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP3A4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td></td>
<td>Warfarin</td>
<td>Plavix</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td>Phenytoin &amp; Valproic acid</td>
<td>Carisoprodol</td>
<td>Fluticasone</td>
</tr>
<tr>
<td>SSRIs &amp; TCAs</td>
<td></td>
<td>Fluoxetine</td>
<td>Diazepam</td>
<td>Cyclosporine and Tacrolimus</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td>Sulfonylureas</td>
<td>Proton pump inhibitors</td>
<td>Statins</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td>NSAIDs</td>
<td>SSRIs &amp; TCAs</td>
<td>Combined Oral Contraceptives</td>
</tr>
</tbody>
</table>

# Phenotype frequency

## Table 8. Individuals with one or more variation in each particular CYP450.

<table>
<thead>
<tr>
<th></th>
<th>Current study</th>
<th>Villagra et al. [33]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variations</td>
<td>67 (5.9%)</td>
<td>7.4%</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>214 (18.7%)</td>
<td>32.9%</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>107 (9.4%)</td>
<td>4.9%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>36 (3.1%)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Subtotal (variations in one CYP)</td>
<td>357 (31.2%)</td>
<td>41.0%</td>
</tr>
<tr>
<td>2D6+2C19</td>
<td>394 (34.5%)</td>
<td>25.2%</td>
</tr>
<tr>
<td>2D6+2C9</td>
<td>180 (15.7%)</td>
<td>19.1%</td>
</tr>
<tr>
<td>2C19+2C9</td>
<td>31 (2.7%)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Subtotal (variations in two CYPs)</td>
<td>605 (52.9%)</td>
<td>45.0%</td>
</tr>
<tr>
<td>2D6+2C9+2C19</td>
<td>114 (10.0%)</td>
<td>6.6%</td>
</tr>
<tr>
<td>Total</td>
<td>1143 (100.0%)</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Data from 14578 patients tested at Genelex

Distribution of abnormal phenotypes in 5-panel tested patients (n=14578)

Source: Data from 14578 patients tested at Genelex
### Translating PGx into Health Outcomes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>PM</th>
<th>IM</th>
<th>EM</th>
<th>UM</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug to inactive metabolite</td>
<td>High toxicity</td>
<td>High toxicity</td>
<td>Normal profile</td>
<td>Low efficacy</td>
<td>metoprolol (CYP2D6) celecoxib (CYP2C9)</td>
</tr>
<tr>
<td>Prodrug to active metabolite</td>
<td>Low efficacy No to low toxicity</td>
<td>Low efficacy</td>
<td>Normal profile</td>
<td>High toxicity</td>
<td>codeine and tramadol (CYP2D6)</td>
</tr>
<tr>
<td>Drug to toxic metabolite</td>
<td>No to low toxicity</td>
<td>No to low toxicity</td>
<td>Normal profile</td>
<td>High toxicity</td>
<td>inhalation anesthetics (CYP2E1)</td>
</tr>
</tbody>
</table>
CYP2D6 phenotype effects on nortriptyline pharmacokinetics

20,534 patients and 16,193 interactions reaching a severity rating of change or consider.
Indication for Testing

1. Therapeutic drug monitoring (TDM) and blood levels are not within normal limits (WNL).
   • Furthermore, this cannot be explained by other factors such as compliance, malabsorption, DDI, etc.
   • This could include urine drug screen results

2. Patient has in the past or is currently experiencing adverse effect or sub-optimal effect to a medication metabolized by this enzyme/biomarker.
   • Furthermore, this cannot be explained by other factors such as compliance, malabsorption, DDI, etc.

3. Patient is initiating a drug metabolized by this enzyme.
   • The strongest case can be made for drugs with established clinical validity, like those with CPIC guidelines (i.e. clopidogrel, warfarin, simvastatin and SLCO1B1, etc.)
INTERACTIONS
Glossary

- **Substrate** – compound that is metabolized by a given enzyme
- **Inhibitor** – slows down or stops the metabolism of a substrate by a given enzyme
  - Mechanism based
  - Competitive based
- **Inducer** – speeds up the metabolism of a substrate by a given enzyme
Drug Interactions: Inhibition

Common CYP2D6 inhibitors:
- fluoxetine
- paroxetine
- bupropion
- duloxetine
- quinidine
Induction

Inducing drug (blue)

Affected drug (yellow)

Common inducers:
- phenytoin
- primidone
- phenobarbital
- carbamazepine
- rifampin
- St. John’s Wort
- cigarette smoking
Six Patterns of Interactions

1. Substrate added to an inhibitor
2. Substrate added to an inducer
3. Inhibitor added to a substrate
4. Inhibitor removed from a substrate
5. Inducer added to a substrate
6. Inducer removed from a substrate

Immediate
1 to 5 days
Weeks
Six Patterns of Interactions

Immediate

Intermediate: 1 to 5 days

Delayed: up to several weeks

Scott et. al 2003
CASES
Pattern 1 - confusion

- Chlor-Trimeton® (chlorpheniramine)
- Major CYP2D6 substrate
- CYP2D6 Poor Metabolizer
- Study shows 200% increase in CYP2D6 Poor Metabolizers
- Patient stopped drug
- 3 days later she called to say she had been in a drug induced haze and could now think clearly again
Pattern 2 - Abdominal migraine

- Cyclic vomiting syndrome

- Treatment of choice is amitriptyline

- UpToDate guidelines state, “Some CVS pts who do not respond to 1 mg/kg per day have very low or undetectable blood levels of amitriptyline, and respond when the dose is further increased.”

http://www.stmgb.org/Scripts/pageview.asp?id=320

UpToDate accessed 5/14/15
Pattern 3: Codeine toxicity

- 62 yo pt with chronic lymphocytic leukemia
- Three day hx of fatigue, dyspnea, fever & cough
- Meds:
  - Valproic acid 1500 mg daily
- Admitted and following meds initiated:
  - ceftriaxone
  - clarithromycin
  - voriconazole
  - codeine 25 mg TID for cough
- Day four: found unresponsive → sent to ICU
  - Rapid improvement with naloxone
  - Recovered after two days

Pattern 4: Methadone treatment failure

- 32 yo heroin addict
- Enrolled in substance abuse program
- Medications:
  - Methadone 80 mg/ day
  - Bupropion (Wellbutrin®) 150 mg BID
- Not satisfied with methadone replacement therapy and anxious
- Bupropion was discontinued because of anxiety
- Pt relapsed on heroin several days later
- CYP2D6 Ultra Rapid Metabolizer

http://www.kitsapsun.com/photos/galleries/2011/mar/12/methadone-treatment/16473/#axzz2KLRqGV8c
Pattern 5: Unplanned parenthood

- 25 yo pt gets pregnant two months after starting carbamazepine (Tegretol®, Equetro®) for Bipolar Mania
- Medications:
  - Carbamazepine 800 mg/ day
  - Levonorgestrel 0.15 mg/ ethinyl estradiol 30 mcg (Portia®, Altavera®, etc.) daily
- Experienced break through bleeding but did not mention to health care provider

Pattern 6: Delayed toxicity

- Pt suffered from reversible respiratory depression
- Was receiving:
  - methadone 120 mg/day for chronic pain management due to advanced lung cancer and dorso-lumbar bone metastases
  - gabapentin (Neurontin®) 900 mg/day for neuropathic pain
- 11 days earlier carbamazepine (Tegretol®) 1200 mg/day for neuropathic pain was stopped due to ataxia
- The methadone dose was not adjusted
- Improvement with naloxone
## Case: Opioid Diversion?

<table>
<thead>
<tr>
<th>Test</th>
<th>Flag Results</th>
<th>Unit</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation - Opiates</td>
<td>Positive</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Codeine</td>
<td>Negative</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Positive</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Negative</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Morphine</td>
<td>Negative</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Negative</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Negative</td>
<td>ng/mL</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>
TIE IT ALL TOGETHER
Clinical take home points

• Always include ADR on differential problem list
• Look for the last medication added or removed as the culprit
• Remember that the change could have been recent or up to several weeks back
• Remember the interplay between drugs and genetics
• When making changes try to change just one drug at a time
• There are too many interactions to rely on our own memory, software is essential to identify and predict them
• Start low and go slow
DNA Testing Companies

- Physicians Choice Laboratory Services (PCLS) [http://www.pcls.com/](http://www.pcls.com/)
- Vantari [http://www.vantarigenetics.com/about.php](http://www.vantarigenetics.com/about.php)
SUPPLEMENTAL SLIDES
PHARMACODYNAMIC BIOMARKERS
“What the drug does to the body”
List of Pharmacodynamic Biomarkers

- **MTHFR**
  - Thrombosis risk, cardiovascular risk, methotrexate and folic acid metabolism
- **Factor II (F2)**
  - Thrombosis risk
- **Factor V Leiden (F5)**
  - Thrombosis risk
- **OPRM1**
  - Opioid response, naltrexone response, addiction risk
- **VKORC1**
  - Warfarin sensitivity
- **IFNL3**
  - Response to pegylated interferon-alpha
Questions???