PHARMACOGENETICS: IS THE PROMISE OF PERSONALIZED MEDICINE FINALLY A REALITY?

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PROVIDENCE MEDICAL GROUP

OBJECTIVES

• Describe the potential benefits of (and barriers to) incorporating pharmacogenetic results into prescribing decisions
• Identify the most common medications that may be affected by genetic variations
• Interpret and apply pharmacogenetic test results

Conflicts of interest: None
Raise your hand if you feel comfortable ordering a pharmacogenetic test and interpreting the results?

A PGX PRIMER

• Pharmacogenetics (PGx) is the study of how genetic variation changes an individual’s response to a medication
• A single nucleotide polymorphism (SNP) is the most common type of genetic variation
• If a SNP affects the function of a gene that codes for a drug metabolizing enzyme or a drug transporter or a drug target, it can change the pharmacokinetics or pharmacodynamics of a medication
• For some specific gene-drug pairs, there is evidence to support a significant, clinically-relevant association between genetic variability and drug levels or effects
**Phenotype Genetic Mechanisms & Effects**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genetic Mechanisms &amp; Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer</td>
<td>2 inactive alleles → greatly reduced drug metabolism</td>
</tr>
<tr>
<td>Intermediate Metabolizer</td>
<td>2 decreased-activity alleles or 1 inactive allele → less efficient drug metabolism</td>
</tr>
<tr>
<td>Extensive Metabolizer</td>
<td>2 functional alleles → “normal” drug metabolism</td>
</tr>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Gene duplication → increased drug metabolism</td>
</tr>
</tbody>
</table>

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**THE GOAL**

Same prescription for everyone

- **Responders**
  - Treat with “normal” drug and dose

- **Non-Responders**
  - Treat with alternative drug or dose

**Toxic Responders**
PEOPLE DO NOT RESPOND TO DRUGS IN THE SAME WAY...

- Gender
- Age
- Kidney and/or liver function
- Weight/Size
- Drug-drug interactions
- Diet
- Genetic variation

![Diagram of drug metabolism]

**Codeine**

- CYP 3A4
- UGT 2B7
- CYP 2D6

**Norcodeine**

**Codeine-6-glucuronide**

**Morphine**
**CLINICAL IMPACT**

- Tramadol, hydrocodone, and oxycodone are also metabolized to their active forms through CYP2D6
- There have been multiple case reports of codeine-related intoxication and death
  - The FDA recently added a new black box warning and contraindication for the use of codeine and tramadol in children younger than 12 years, and strengthened warnings regarding the use of codeine and tramadol in breastfeeding mothers

https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm
Clopidogrel

2-step metabolic process that is largely dependent on CYP2C19

Inactive metabolite (85% of dose)

Active Metabolite

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2-15%

PM

Significantly reduced platelet inhibition; Recommend ALTERNATIVE antiplatelet therapy

18-45%

IM

Reduced platelet inhibition; Recommend ALTERNATIVE antiplatelet therapy

35-50%

EM

Normal platelet inhibition

5-30%

UM

Increased platelet inhibition
**CLINICAL IMPACT**

- A meta-analysis found that patients who are undergoing a PCI for ACS and who are poor or intermediate CYP2C19 metabolizers and taking clopidogrel have a significantly increased risk of adverse clinical outcomes:
  - Composite outcome of CV death, MI, or stroke
    - **IM**: HR, 1.55; 95% CI, 1.11-2.17; p=0.01
    - **PM**: HR, 1.76; 95% CI, 1.24-2.50; p=0.002
  - Stent thrombosis
    - **IM**: HR, 2.67; 95% CI, 1.69-4.22; p<0.0001
    - **PM**: HR, 3.97; 95% CI, 1.75-9.02; p=0.001
- The FDA added a black box warning in 2010 for poor metabolizers

*JAMA. 2010;304(16):1821-1830*

**SCOPE**

- Pharmacogenetic information is included in the labeling of over 150 medications
- ~100 medications possess potentially “actionable” pharmacogenetic information
  - 7% of FDA-approved medications
  - 18% of US prescriptions
- In a one-year period, ~50% of patients receive at least one pharmacogenetically high risk drug

FDA-APPROVED LABELS WITH ACTIONABLE PGX

- Abacavir/HLA-B
- Aripiprazole/CYP2D6
- Azathioprine/TPMT
- Carbamazepine/HLA-A, HLA-B
- Carvedilol/CYP2D6
- Celecoxib/CYP2C9
- Clopidogrel/CYP2C19
- Codeine/CYP2D6
- Metoprolol/CYP2D6
- Phenytoin/CYP2C9, HLA-B
- PPIs/CYP2C19
- Simvastatin/SLCO1B1
- SSRIs & SNRIs/CYP2C19 and/or CYP2D6
- Tamoxifen/CYP2D6
- Tamsulosin/CYP2D6
- TCAs/CYP2C19, CYP2D6
- Tramadol/CYP2D6
- Warfarin/CYP2C9, VKORC1
- Etc., Etc., Etc.

ACTIONABLE PGX

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Phenotype</th>
<th>Clinical Implication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>CYP2D6</td>
<td>Poor metabolizer</td>
<td>Increased potential for adverse effects</td>
<td>Use alternative therapy or reduce starting dose by 50%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19</td>
<td>Poor Metabolizer</td>
<td>Increased risk of cardiovascular complications related to ACS or PCI</td>
<td>Use alternative Therapy</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Ultra-rapid</td>
<td>Potential for toxicity</td>
<td>Use alternative therapy</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9, VKORC1</td>
<td>CYP2C9 Poor Metabolizer or VKORC Warfarin Sensitive</td>
<td>Increased risk of bleeding</td>
<td>Adjust starting dose</td>
</tr>
</tbody>
</table>
THE V.I.Ps

<table>
<thead>
<tr>
<th>Drug Metabolizing Enzymes</th>
<th>Drug Targets</th>
<th>Drug Transporters</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>CFTR</td>
<td>SLCO1B1</td>
<td>G6PD</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>VKORCI</td>
<td></td>
<td>HLA-B</td>
</tr>
<tr>
<td>CYP2C19</td>
<td></td>
<td></td>
<td>IFNL3</td>
</tr>
<tr>
<td>CYP3A5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPYD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT1A</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

BARRIERS TO IMPLEMENTATION

- Limited evidence of clinical utility
- Lack of guidance for use
- Limited or unclear insurance coverage/reimbursement
- Absence of the appropriate infrastructure
LIMITED EVIDENCE?

• The available evidence is primarily observational and retrospective
  – RCTs are not often practical or even ethical
  – Other dosing decisions are routinely made using similarly “weak” evidence

• It depends on the question:
  – Do I need to order a genetic test?
  – What should I do with this genetic test?

LIMITED EVIDENCE?

• PREPARE (Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions)
  – A large RCT including 8,000 patients in 7 European countries
  – Participants will be pre-emptively tested for more than 40 clinically-relevant PGx markers on 13 genes
  – Patients will be randomized to either receive or not receive pharmacogenetic-led prescribing
  – Results expected in 2020

http://upgx.eu/study/
## CLINICAL GUIDANCE

**CPIC: Clinical Pharmacogenetics Implementation Consortium**
- An international consortium that creates, curates, and posts freely available, peer-reviewed, evidence-based, updateable, and detailed gene/drug clinical practice guidelines (33 so far)

**PharmGKB**
- NIH-funded resource that collects, curates, and disseminates knowledge about the impact of human genetic variation on drug responses

https://cpicpgx.org/
https://www.pharmgkb.org/

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<tr>
<th>Drug Combination</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Abacavir/HLA-B</td>
<td>Desipramine/CYP2D6</td>
<td>Phenytoin/CYP2C9, HLA-B</td>
</tr>
<tr>
<td>Allopurinol/HLA-B</td>
<td>Doxepin/CYP2C19, CYP2D6</td>
<td>Rasburicase/G6PD</td>
</tr>
<tr>
<td>Amitriptyline/CYP2C19, CYP2D6</td>
<td>Fluorouracil/DPYD</td>
<td>Sertraline/CYP2C19</td>
</tr>
<tr>
<td>Atazanavir/UGT1A1</td>
<td>Fluvoxamine/CYP2D6</td>
<td>Simvastatin/SLCO1B1</td>
</tr>
<tr>
<td>Azathioprine/TPMT</td>
<td>Imipramine/CYP2C19, CYP2D6</td>
<td>Tacrolimus/CYP3A5</td>
</tr>
<tr>
<td>Capecitabine/DPYD</td>
<td>Ivacaftor/CFTR</td>
<td>Tegafur/DPYD</td>
</tr>
<tr>
<td>Carbamazepine/HLA-B</td>
<td>Mercaptopurine/TPMT</td>
<td>Thioguanine/TPMT</td>
</tr>
<tr>
<td>Citalopram/CYP2C19</td>
<td>Nortriptyline/CYP2D6</td>
<td>Trimipramine/CYP2C19, CYP2D6</td>
</tr>
<tr>
<td>Clomipramine/CYP2C19, CYP2D6</td>
<td>Ondansetron/CYP2D6</td>
<td>Tropisetron/CYP2D6</td>
</tr>
<tr>
<td>Clopidogrel/CYP2C19</td>
<td>Paroxetine/CYP2D6</td>
<td>Voriconazole/CYP2C19</td>
</tr>
<tr>
<td>Codeine/CYP2D6</td>
<td>Peginterferon, ribavirin/IFNL3</td>
<td>Warfarin/CYP2C9, CYP4F2, VKORC1</td>
</tr>
</tbody>
</table>
ALREADY A REALITY

The gene-by-gene method:
- HLA-B screening for patients with HIV
- TPMT screening for patients with leukemia

ALREADY A REALITY

The disease-state focused method:

- Depression
  - In the STAR*D study only ~1/3 of patients achieved remission during the first step of treatment (citalopram)
  - For those patients who do not readily achieve remission, the odds of doing so decrease with each additional treatment strategy
  - 5 studies have assessed for changes in clinical outcomes (i.e., depression severity, response or remission rates) as a result of prescribing guided by pharmacogenetic testing

**BRADLEY, ET. AL.**

- **Study:** Prospective, randomized trial designed to evaluate the effect of PGx-guided treatment in patients with depression and/or anxiety
- **Population:** n=685 adults, including those new to therapy and those failing current therapy
- **Setting:** 20 clinics in the US, including Psychiatry, Internal Medicine, Obstetrics & Gynecology, and Family Medicine
- **Methods:** PGx results were provided to clinicians for subjects assigned to the experimental group, while control subjects were treated according to standard of care

*Journal of Psychiatric Research, 2018;96:100-107.*

<table>
<thead>
<tr>
<th>GeneSight</th>
<th>Genecept Assay</th>
<th>NeurolDgenetix</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>CYP1A2</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>CYP2B6</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>ADRA2A</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>CYP2C9</td>
<td>OPRM1</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>MC4R</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>CYP3A4/5</td>
<td>MTHFR</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>SLC6A4</td>
<td>HTR2A</td>
</tr>
<tr>
<td>HTR2A</td>
<td>5HT2C</td>
<td>COMT</td>
</tr>
<tr>
<td>UGT1A4</td>
<td>DRD2</td>
<td>MTHFR</td>
</tr>
<tr>
<td>UGT2B15</td>
<td>CACNA1C</td>
<td></td>
</tr>
<tr>
<td>HLA-A</td>
<td>ANK3</td>
<td></td>
</tr>
<tr>
<td>HLA-B</td>
<td>BDNF</td>
<td></td>
</tr>
</tbody>
</table>
In the experimental group, medication changes were aligned with the report recommendations 70% of the time; in the control group, the changes aligned with the report only 29% of the time.

At the 2 week visit, physicians made at least 1 medication change in 81% of subjects in the experimental group, compared to 64% of subjects in the control group (p<0.0001).
BRADLEY, ET. AL.

Patients Achieving Remission
Severe Depression

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>NeurolDgenetix</td>
<td>25%</td>
<td>35%</td>
</tr>
</tbody>
</table>

p = 0.02
OR: 3.54, NNT = 5


BRADLEY, ET. AL.

Patients Achieving Response
Severe Depression

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>NeurolDgenetix</td>
<td>55%</td>
<td>73%</td>
</tr>
</tbody>
</table>

p = 0.001
OR: 4.72, NNT = 3

ALREADY A REALITY

The pre-emptive method:
- St. Jude Children’s Research Hospital
- Mayo Clinic
- Mt. Sinai Medical Center (New York)
- Vanderbilt University Medical Center
- University of Florida and Shands Hospital

• Gene/drug pairs with sufficient evidence for clinical use are included in the electronic health record
• Prescribers are provided with clinical decision support

COST EFFECTIVE?


DF, 50 YO FEMALE

- DF presents for a follow-up office visit
- PMH significant for VTE x 2, HTN, DM, osteoarthritis, migraines, and depression
- Medications:
  - Amlodipine
  - Butalbital/ASA/Caffeine/Codeine
  - Chlorthalidone
  - Citalopram
  - Glimepiride
  - Metformin
  - Simvastatin
  - Warfarin

**Gene Alleles Phenotype**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alleles</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>*1/*1</td>
<td>Extensive (Normal) Metabolizer</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*17/*17</td>
<td>Ultrarapid Metabolizer</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*2</td>
<td>Intermediate Metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*4/*4</td>
<td>Poor Metabolizer</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>Extensive (Normal) Metabolizer</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>*5/*5</td>
<td>Poor Function</td>
</tr>
</tbody>
</table>

Avoid due to lack of efficacy
Consider an alternative due to lack of efficacy
High myopathy risk
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