Managing Heterogenous Treatment Effects: The Case for Pharmacogenomics

National Academy of Sciences

Evidence and the Individual Patient: Understanding Heterogenous Treatment Effects for Patient-Centered Care.

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DEPT. BIOMEDICAL INFORMATICS AND MEDICINE
### Table 3. Rates of Adverse Drug Events.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse Events</th>
<th>Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no./100 patients</td>
</tr>
<tr>
<td>Total adverse drug events</td>
<td>181</td>
<td>27.4</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal or life-threatening</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Serious</td>
<td>24 (13)</td>
<td>3.6</td>
</tr>
<tr>
<td>Significant</td>
<td>157 (87)</td>
<td>23.8</td>
</tr>
<tr>
<td>Preventability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ameliorable</td>
<td>51 (28)</td>
<td>7.7</td>
</tr>
<tr>
<td>Preventable</td>
<td>20 (11)</td>
<td>3.0</td>
</tr>
<tr>
<td>Not preventable</td>
<td>110 (61)</td>
<td>16.6</td>
</tr>
</tbody>
</table>

* Percentages may not sum to 100, because of rounding.

- **Serious Cutaneous Adverse Reaction (SCAR)**
- **SSRI Side Effects**
- **NSAID related GI Event**
- **Beta-blocker related bradycardia**
Carbamazepine associated Stevens Johnson Syndrome in patients with a HLA-B*1502
# Suboptimal Drug Efficacy

Percentage of the patient population for which a particular drug in a class is ineffective, on average:

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants (SSRIs)</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
</tbody>
</table>

*The Case for Personalized Medicine, 2014*
Predicting and Optimizing Drug Response

Age
Renal clearance
Drug interactions
Pharmacogenomics
Indication for therapy
Behavioral factors
## Spectrum of Evidence in Pharmacogenomics

<table>
<thead>
<tr>
<th>Analytic Validity</th>
<th>Clinical Validity</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel platform validation</td>
<td>GWAS</td>
<td>Randomized Controlled Trials</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>PheWAS</td>
<td>Comparative Effectiveness</td>
</tr>
<tr>
<td></td>
<td>Correlation with phenotypic testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Candidate gene study of clinical outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Observational</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Genetic Sub-study RCT</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Platelet aggregation (absolute values) in response to 10 μM ADP according to the *CYP2C19*/*2* genotype. Absolute values at baseline (A) and after 6 days (day 7) of clopidogrel 75 mg/d (B). The line indicates the mean value.
CYP2C19 Variants and Clopidogrel Treated ACS Patients Undergoing PCI (TRITON TIMI-38)
Genetic (CYP2C19) Sub-study of PLATO (Clopidogrel vs Ticagrelor)

Time to Major Adverse Coronary Event
Multi-Site Comparative Effectiveness of CYP2C19-Guided Antiplatelet Therapy

Cavallari, JACC: Cardiovascular Interventions 2018
Pragmatic Randomized Controlled Trials

Genotype (TPMT) Guided Azathioprine vs “Usual Care”

Newman, Pharmacogenomics 2011
Pharmacogenomics: PREDICT Model

Target Clinics

Prognostic Flag for Testing

Preemptively Tested

Reactive/Indication Testing

Genotyped for PREDICT

- CYP2C19 Variant
- SLC01B1 Variant
- VKORC1 + CYP2C9

Clinical Application

- Clopidogrel
- Simvastatin
- Warfarin

Genotyping

Genetic Risk

Has genetic risk variant

Exposed to new or recent prescription
Making Evidence-Based Program Decisions

Abstract CPIC Guideline
→ Engage Clinical Experts
→ Review and Approval by Lab Formulary
## Translating Genetic Nomenclature

### Simvastatin and SLC01B1 interaction

<table>
<thead>
<tr>
<th>Result</th>
<th>Gene</th>
<th>Nucleotide variation</th>
<th>Effect on SLC01B1 protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLC01B1</td>
<td>rs4149056</td>
<td>Decreased transporter function</td>
</tr>
</tbody>
</table>

### Genotype & Phenotype

SLC01B1 *5/*5

Simvastatin High Myopathy Risk

### Interpretation

Prescribe a dose of 20mg or lower or consider an alternative statin; consider routine CK surveillance.
Drug-Gene Interaction

**Clopidogrel Intermediate Metabolizer Rules**

**Genetic testing has been performed and indicates this patient may be at risk for inadequate anti-platelet response to clopidogrel (Plavix) therapy**

This patient has been tested for CYP2C19 variants, which has identified the presence of one copy of a risk allele which is associated with poor metabolism of clopidogrel. Intermediate metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

**Treatment modification is recommended if not otherwise contraindicated:**
- Prescribe ticagrelor (BRILANITA) 90 mg twice daily

Ticagrelor should **not** be given to patients that have a history of severe hepatic impairment or intracranial bleed

**Evidence Link**

The Vanderbilt P&T Committee has approved this recommendation based on the detailed review of the literature and consensus guidelines.

**Remove** the following orders?

- **Remove** clopidogrel (PLAVIX) 75 mg tablet
  - Take 1 tablet (75 mg total) by mouth daily. Normal, Disp. 30 tablet, R.11

**Apply** the following?

- Order prasugrel (EFFIENT) tablet 10 mg
- Order ticagrelor (BRILINTA) tablet 90 mg

**Accept**  **Dismiss**
Example: Warfarin Advisor

Warfarin Recommended Initial Dosing

This patient has been tested for CYP2C9 and VKORC1 genetic variants that can affect a patient's warfarin dosing requirements. The following dosing algorithm uses genetic and other patient information to estimate a weekly warfarin dose. This dosing recommendation ONLY applies to NEW starts of warfarin. If the patient has previously taken a stable dose of warfarin, please disregard this dosing recommendation.

- **Age:** 56
- **Weight (kg):** 77.1
- **Height (cm):** 175.3
- **Genetic Variants:** vkorc1 a/a; cyp2c9 *2/*2;
- **Is the patient currently taking amiodarone?** No
- **Is the patient currently taking Phenytoin, Rifampin, or Carbamazepine?** No

**Recommended WEEKLY starting dose of warfarin: 16.8 mg/week**

The DAILY equivalent of this recommended starting dose is 2.4 mg/day.

NOTE: Further dose adjustments may be necessary due to other clinical factors, such as diet and other interacting medications (e.g., antibiotics or antifungals). This algorithm ONLY considers age, height, weight, genetic factors, and select medications (amiodarone, rifampin, phenytoin, and carbamazepine).

[Help me decide the tablet size and number of tablets per day](Evidence Link/View Algorithm)
Personalized Medicine

Each person responds differently to medicines. Your genes play a role in how you respond to medicines. Based on your history, your provider has ordered a test to learn more about which drugs are right for you. Having this information can help predict and prevent bad drug side effects.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Does your genetic test result affect your response to medicines?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel/Plavix®</td>
<td>Yes</td>
</tr>
<tr>
<td>Simvastatin/Zocor®</td>
<td>Yes</td>
</tr>
<tr>
<td>Tacrolimus®</td>
<td>Yes</td>
</tr>
<tr>
<td>Thiopurine Therapy®</td>
<td>Yes</td>
</tr>
<tr>
<td>Warfarin/Coumadin®</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The Clopidogrel Test

Clopidogrel (sounds like "kloh-PID-oh-gral") is a blood thinner used to prevent clots that can cause a heart attack or stroke. Your genes can affect how well the drug works. This genetic test identifies how well you may respond to clopidogrel.

Your Risk

Sometimes clopidogrel does not prevent harmful strokes or clots as well as it should because of your genes. Your provider, often with the results of a lab test, can determine if clopidogrel is the right medicine for you.

The results of your test show that you have two versions of the gene that may put you at increased risk for this negative outcome.

More About Clopidogrel

More About Your Risk
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