Combinatorial Pharmacogenomic Algorithm is Predictive of Citalopram and Escitalopram Metabolism in Patients with Major Depressive Disorder

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**BACKGROUND**

- Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) for citalopram and escitalopram dosing depend on metabolism phenotype classifications derived only from genetic variations in CYP2C19, likely because evidence for the contribution of other enzymes to their metabolism was limited.
- Compatibly, a combinatorial pharmacogenomic (PGx) test makes independent citalopram dosing recommendations based on a combined metabolism phenotype derived from CYP2C19, CYP2D6, and CYP3A4.
- We determined the validity of combinatorial PGx testing by assessing blood levels of citalopram from PGx test recommendations and CYP2C19 phenotype classifications.

**METHODS**

**COHORT**

- The following is a subanalysis of the Genomics Used to Improve DEpression Decisions (GUIDED) randomized, controlled trial assessing the utility of combinatorial PGx testing in depression.
- 191 out of 1,167 patients reported taking citalopram or escitalopram within 2 weeks of the screening blood draw and had citalopram blood concentrations quantified using LC-MS/MS.

**COMBINATORIAL PGx TESTING**

- Multiple genotypes were weighted to produce a combined phenotype.
- Medications were categorized by the severity of gene-drug interactions (GDI): none/weak, moderate, and significant.

**STATISTICAL ANALYSIS**

- Blood levels of citalopram were assessed according to:
  1. CYP2C19 alone: combinatorial PGx test phenotype versus CYP2C phenotype
  2. CYP2C19 alone versus the combinatorial PGx test
  3. Multivariate analysis of CYP2C19 alone and combinatorial PGx test
- Analysis of covariance (ANCOVA) tests with categorical genetic variables were used to assess the relationship between blood levels and genetic variables.
- ANCOVA tests with numerically transformed genetic variables were used to compare the variability explained by the recommendations from CPIC guidelines and from the combinatorial PGx test.

**RESULTS**

**CONCLUSIONS**

- CYP2C19 phenotypes from the combinatorial PGx test more accurately reflected citalopram blood levels than those from CPIC guidelines.
- The additional impact of CYP2D6 and CYP3A4 contributed to the validity of the combinatorial PGx test.
- Combinatorial PGx testing allows for more patients to receive clinically actionable dosing guidance than single-gene classifications.

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**Table 1. Evaluation of individual genes and the combinatorial pharmacogenomic test to predict variance in citalopram and escitalopram blood level**

<table>
<thead>
<tr>
<th>Variables included in Model*</th>
<th>Individual Genes</th>
<th>Combinatorial PGx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F Statistic</strong></td>
<td><strong>p-value</strong></td>
<td><strong>F Statistic</strong></td>
</tr>
<tr>
<td>Combinatorial PGx Test</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CYP2C19 Alone**</td>
<td>7.8</td>
<td>0.0066</td>
</tr>
<tr>
<td>CYP2C19 Alone†</td>
<td>6.8</td>
<td>0.01</td>
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<tr>
<td>Combinatorial PGx + CYP2C19**</td>
<td>2.5</td>
<td>0.12</td>
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<tr>
<td>Combinatorial PGx + CYP2C19†</td>
<td>0.21</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*All models included patient age and smoking status CYP2C19

** Phenotypes assigned using CPIC guidelines

** Combinatorial PGx phenotypes assigned as part of combinatorial PGx testing were used

**The additional impact of CYP2D6 and CYP3A4 contributed to the validity of the combinatorial PGx test.**

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