Using Pharmacogenomics to Inform Depression Treatment

Holly Johnson, Ph.D.
Unmet Medical Need from Treatment As Usual

Less than 40% of patients achieve remission with initial drug treatment. With each additional medication trial, the chance of remission decreases, while treatment intolerance increases.

<table>
<thead>
<tr>
<th># of Medication Treatments</th>
<th>Remission Rate</th>
<th>Intolerance Rate (Side Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37%</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>14%</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>13%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Why Are They Failing?

Here are some of the usual culprits:
- Adherence
- Environmental Factors
- Cost / Insurance
- Adverse Effects

But have you considered that genetic variability may undermine medication choices and may be a factor in treatment failure?
Personalized Medication Selection Factors

- Patient experience
- Pharmacogenomics
- Illness
- Adherence
- Adverse effects
- Family history
- Cost
Pharmacodynamics and Pharmacokinetics

Pharmacodynamic variation changes how the drug affects the body

Pharmacokinetic variation changes how the body affects the drug

Systemic Circulation

Excretion
**How Genetics Can Affect Medication Blood Levels**

### Phenotypes

**Ultrarapid Metabolizer**  
Breaks down medications rapidly. May not get enough medication at normal doses.

**Extensive (Normal) Metabolizer**  
Breaks down medications normally. Has normal amounts of medication at normal doses.

**Intermediate Metabolizer**  
Breaks down medications slowly. May have too much medication at normal doses.

**Poor Metabolizer**  
Breaks down medications very slowly. May experience side effects at normal doses.
# The GeneSight® Psychotropic Report

## GeneSight® Psychotropic
Pharmacogenomic Test

<table>
<thead>
<tr>
<th>Patient, Sample</th>
<th>Order Number: 3740219</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth: 7/22/1984</td>
<td>Report Date: 5/12/2021</td>
</tr>
<tr>
<td>Clinician: Sample Clinician</td>
<td>Reference: 145CIP</td>
</tr>
</tbody>
</table>

### Questions about report interpretation?
Contact our medical information team:
855.891.9415 | medinfo@genesight.com

## Antidepressants

### Use as Directed
- desvenlafaxine (Pristiq®)
- levomilnacipran (Fetzima®)
- vilazodone (Viibryd®)

### Moderate Gene-drug Interaction
- trazodone (Desyrel®) 1
- venlafaxine (Effexor®) 1
- fluoxetine (Prozac®) 1,4
- bupropion (Wellbutrin®) 1,6
- citalopram (Celexa®) 3,4
- escitalopram (Lexapro®) 3,4

### Significant Gene-drug Interaction
- selegiline (Emsam®) 2
- mirtazapine (Remeron®) 1,6
- sertraline (Zoloft®) 2,4
- amitriptyline (Elavil®) 1,6,8
- clomipramine (Anafranil®) 1,6,8
- desipramine (Norpramin®) 1,6,8
- doxepin (Sinequan®) 1,6,8
- duloxetine (Cymbalta®) 1,6,8
- imipramine (Tofranil®) 1,6,8
- nortriptyline (Pamelor®) 1,6,8
- vortioxetine (Trintellix®) 1,6,8
- fluvoxamine (Luvox®) 1,4,6,8
- paroxetine (Paxil®) 1,4,6,8
What are the Clinical Considerations?

Clinical Considerations
These state rationale for a medication’s classification and offer treatment adjustments if a clinician desires to use this medication.

Clinical Considerations
1: Serum level may be too high, lower doses may be required.
2: Serum level may be too low, higher doses may be required.
3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
4: Genotype may impact drug mechanism of action and result in moderately reduced efficacy.
6: Use of this drug may increase the risk of side effects.
8: FDA label identifies a potential gene-drug interaction for this medication.
Interpreting **Combinatorial** Pharmacogenomic Testing Can Get Complex

<table>
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<tr>
<th>Pharmacokinetic Markers</th>
<th>Pharmacodynamic Markers</th>
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<tbody>
<tr>
<td>CYP2D6</td>
<td>ADRA2A</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19</td>
<td>HLA-A*3101</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2</td>
<td>HLA-B*1502</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4</td>
<td>HTR2A</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4 + CYP2B6</td>
<td>SLC6A4</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4 + CYP2B6 + UGT1A4</td>
<td></td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4 + CYP2B6 + UGT1A4 + UGT2B15 + CES1A1</td>
<td></td>
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1,990,656 resultant composite phenotypes based on the 14 genes in the GeneSight® algorithm
Psychotropic Medications Are Processed Through Multiple Genetic Pathways

**Pharmacodynamic Genes**
- HLA-A*3101
- HLA-B*1502
- SLC6A4
- HTR2A
- ADRA2A

**Pharmacokinetic Genes**
- CYP2D6
- CYP2C19
- CYP2C9
- CYP3A4
- CYP2B6
- CYP1A2
- UGT1A4
- UGT2B15
- CES1A1
Medications Often Work Through a Unique Combination of These Genetically Controlled Pathways

- Fluoxetine (Prozac®)
- Bupropion (Wellbutrin®)
- Vortioxetine (Trintellix®)
- Paroxetine (Paxil®)
- Duloxetine (Cymbalta®)
- Vilazodone (Viibryd®)
- Escitalopram (Lexapro®)
The Significance of Those Genes Varies by Medication

Fluoxetine (Prozac®)

SLC6A4  CYP2D6  CYP2C19  CYP2C9  CYP3A4
A Patient’s Unique Genetics Impact the Activity Level of Those Pathways

Fluoxetine (Prozac®)

- CYP2C19
- CYP2D6
- CYP2C9
- SLC0A4
- CYP3A4
The GeneSight® Psychototropic Report Categorizes Medications and Provides Clinical Considerations Based on a Combined Assessment of the Drug’s Pharmacology and the Relevant Genetic Pathways

Significant Gene-Drug Interaction

| Fluoxetine (Prozac®) | 1,6 |

Clinical Considerations
1: Serum level may be too high, lower doses may be required.
6: Use of this drug may increase risk of side effects.
The GeneSight® Psychotropic Test Analyzes All 61 Medications on Our Panel Using This Approach

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|                          |                                | doxepin (Sinequan®)              |
|                          |                                | duloxetine (Cymbalta®)           |
|                          |                                | imipramine (Tofranil®)           |
|                          |                                | nortriptyline (Pamelor®)         |
|                          |                                | vortioxetine (Trintellix®)       |
|                          |                                | fluvoxamine (Luvox®)             |
|                          |                                | paroxetine (Paxil®)              |

Order Number: 3740219
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GeneSight® is Easy to Implement in Practice

**Step 1**  
Place your order on myGeneSight.com.

**Step 2**  
You or a member of your staff collect the patient’s DNA sample with a simple cheek swab  
OR  
your patient collects the sample at home using our patient collection kit.

**Step 3**  
Your patient’s sample is sent to our lab for analysis. After the sample is received, results are typically available in about 2 days.

**Step 4**  
Use the genetic insights from the GeneSight report to inform your treatment.
GeneSight® Supports Improved Outcomes in MDD

Identifies medications with significant gene-drug interactions (GDIs) to inform prescribing

10 clinical utility publications demonstrating improvement in patient outcomes \(^1\)\(^{-10}\)

Level 1 evidence demonstrating 49% relative improvement in remission \(^{10}\)

Saved >$1,000 in total annual medication costs compared to treatment as usual \(^{11}\)

Note: Not all patients who receive the GeneSight test will achieve remission or experience cost savings.

GeneSight® Arm Realized a Significant Improvement in All Outcomes

**Level 1 evidence**: Relative improvement in patient outcomes compared to TAU

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Improvement</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>HAM-D17 score ≤7</td>
<td>49%</td>
<td>0.001</td>
</tr>
<tr>
<td>Response</td>
<td>≥50% reduction in HAM-D17 score</td>
<td>40%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom Improvement</td>
<td>Avg % decrease in HAM-D17</td>
<td>43%</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Note: Not all patients who receive the GeneSight test will experience remission, response, or symptom improvement. Brown LC, et al. Pharmacogenomics. 2020 Jun;21(8):559-569.
Patients in the GeneSight® Arm had Lower Total Annual Medication Costs Compared to TAU*¹

GeneSight helped to increase adherence and reduce polypharmacy

- Patients in the GeneSight arm stayed on a new medication 46% longer
- 20% of patients were on fewer medications

*¹ Not all patients who receive the GeneSight Psychotropic test will experience cost savings.
Questions? Comments?
Feedback on this presentation?

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