How Genetic Testing Can Help with Depression Treatment

Holly Johnson, Ph.D.
Ronni Shapiro
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Holly Johnson, Ph.D.
Senior Manager, Medical Information
What Your Doctor Considers Before Prescribing Medication Today

- Medication selection
- Patient experience
- Adverse effects
- Family history
- Cost
- Illness
- Adherence

Medication selection
This Approach Doesn’t Always Work

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.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial

<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 Don’t These Medications Work?

Here are some of the usual culprits:

- Adherence
- Environmental Factors
- Cost / Insurance
- Adverse Effects

Our unique genetic makeup may undermine medication choices and may be a factor in why medications may not work.
Pharmacogenomics Defined

Pharmacogenomics is a field of research that studies how a person’s genes affect how he or she responds to medications.

National Institute of General Medical Sciences
Medication Selection Using Genetic Information

- Patient experience
- Adherence
- Illness
- Cost
- Family history
- Adverse effects
- Pharmacogenomics

Personalized Medication Selection
The GeneSight® Psychotropic Report

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

Patient, Sample
DOB: 7/22/1984
Order Number: 219
Report Date: 8/5/2020
Clinician: Sample Clinician
Reference: 1456CIP

ANTIDEPRESSANTS

USE AS DIRECTED
- desipramine (Norpramin®)
- nortriptyline (Pamelor®)
- vortioxetine (Trintellix®)

MODERATE GENE-DRUG INTERACTION
- doxepin (Sinequan®) 1
- imipramine (Tofranil®) 1.6
- desvenlafaxine (Pristiq®) 1.8
- trazodone (Desyrel®) 1.8
- mirtazapine (Remeron®) 3.7,8

SIGNIFICANT GENE-DRUG INTERACTION
- amitriptyline (Elavil®) 1.6
- bupropion (Wellbutrin®) 1.6
- clomipramine (Anafranil®) 1.6
- fluoxetine (Prozac®) 1.6
- selegiline (Emsam®) 1.6
- duloxetine (Cymbalta®) 2.7
- fluvoxamine (Luvox®) 2.7
- citalopram (Celexa®) 1.4,6
- escitalopram (Lexapro®) 1.4,6
- paroxetine (Paxil®) 1.4,6
- sertraline (Zoloft®) 1.4,6
- levomilnacipran (Fetzima®) 1.6,8
- venlafaxine (Effexor®) 1.6,8
- vilazodone (Viibryd®) 1.6,8

Questions about report interpretation?
Contact our Medical Information team
📞 855.891.9415
✉️ medinfo@assurexhealth.com

Company Confidential
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What are the Clinical Considerations?

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 reduced efficacy.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.
Pharmacodynamics and Pharmacokinetics

Pharmacodynamic variation changes how the drug affects the body

Pharmacokinetic variation changes how the body affects the drug

Systemic Circulation

Excretion
### GeneSight® Psychotropic

#### Pharmacokinetic (PK)
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2
- CYP2B6
- CYP3A4
- UGT1A4
- UGT2B15

#### Pharmacodynamic (PD)
- SLC6A4
  (Serotonin Transporter)
- 5HTR2A
  (Serotonin 2A Receptor)
- HLA-B*1502
  (Human Leukocyte Antigen)
- HLA-A*3101
  (Human Leukocyte Antigen)

GeneSight Psychotropic only tests for genes that have a variant that has a significant impact on medication outcomes, as demonstrated in multiple well-designed studies\(^1\), and appears at a high enough frequency to be clinically meaningful.

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1. [https://genesight.com/references](https://genesight.com/references)
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 serotonin transporter is encoded by the SLC6A4 gene.

It is responsible for reuptake of serotonin into the presynaptic neuron.

Selective serotonin reuptake inhibitors (SSRIs) inhibit this process, allowing for more serotonin in the synaptic cleft.
The Serotonin Transporter

The SLC6A4 promoter has two main variants: short (S) and long (L)\(^1\).

**HTR2A**

HTR2A encodes the serotonin 2A receptor, one of the principal excitatory receptors in the serotonin system.

Studies show increased risk for adverse effects with paroxetine in patients who are homozygous for the G allele.\(^1\)\(^2\)\(^3\)

*Phenotype frequency is based on internal Myriad Neuroscience data of over 700,000 tested patients.
Human Leukocyte Antigen (HLA)

Carbamazepine, oxcarbazepine, and lamotrigine: three medications most commonly associated with severe skin reactions\(^1\)\(^-\)\(^3\)

Meta-analysis of 20 studies found certain HLA alleles significantly overrepresented in patients showing CBZ-induced severe skin reactions\(^4\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA-A*3101</th>
<th>HLA-B*1502</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol(^\circ))(^1)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal(^\circ))(^2)</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal(^\circ))(^3)</td>
<td>-</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Subcategorized by Severity of Skin Reactions**

<table>
<thead>
<tr>
<th></th>
<th>HLA-A*3101 (OR)</th>
<th>HLA-B*1502 (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS/TEN</td>
<td>5.65</td>
<td>80.70</td>
</tr>
<tr>
<td>Less Severe Skin Reactions</td>
<td>8.58</td>
<td>NS for predictive value</td>
</tr>
</tbody>
</table>

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Interpreting **Combinatorial** Pharmacogenomic Testing Can Get Complex

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<tr>
<th>Pharmacokinetic Markers</th>
<th>Pharmacodynamic Markers</th>
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<tbody>
<tr>
<td>CYP2D6</td>
<td>SLC6A4</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19</td>
<td>HTR2A</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2</td>
<td>HLA-B*1502</td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4</td>
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**331,776**

Resultant Composite Phenotypes
Medications Often Work Through a Unique Combination of These Genetically Controlled Pathways

Fluoxetine (Prozac®)

Bupropion (Wellbutrin®)

Vortioxetine (Trintellix®)

Paroxetine (Paxil®)

Duloxetine (Cymbalta®)

Vilazodone (Vlibryd®)

Escitalopram (Lexapro®)

SLC6A4, CYP2D6, CYP2C19, CYP2C9, CYP3A4

CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6

CYP2D6, CYP2C19, CYP2C9, CYP3A4

SLC6A4, HTR2A, CYP2D6, CYP3A4

CYP2D6

CYP2D6, CYP2C9, CYP3A4

SLC6A4, CYP2D6, CYP2C19, CYP3A4
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®)

- High Activity
  - CYP2C19
- Normal
  - SLC0A4
  - CYP2D6
- Low Activity
  - CYP2C9
  - CYP3A4
The GeneSight® Psychotropic 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®)**

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 57 Medications on Our Panel Using This Approach

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### GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

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Talk to your own doctor about ordering the GeneSight test.

Use our Discussion Guide to help with the conversation.

Use our Find a Provider Portal to see who may be using the GeneSight test in your area.
Tips for Talking to Your Doctor about the GeneSight® Test

Be Prepared

Take along any information the doctor or staff may need to see, like names and contact information of your past/other clinicians, records showing past medications or current medications for other conditions, or dietary supplements.

Be Open and Confident

Don’t be afraid to share how your current depression treatment is working for you and where it may be falling short.

Bring a Friend

The support of a friend or family member can help facilitate the conversation with your doctor and help act as a co-advocate for your care at your next appointment.

Discuss Ordering the Test

If you are interested in the GeneSight test, discuss whether you might be a good candidate with your doctor.
Not Able to See Your Doctor in Person? No Problem.

The GeneSight® test can be ordered by your healthcare provider and sent directly to you.

If you need help finding a healthcare provider, you can use the GeneSight Find a Provider tool on our website.
Five Things to Know about the GeneSight® Test

- The results of the test can inform your doctor about genes that may impact how you metabolize or respond to certain medications.

- The GeneSight test is intended to supplement other information considered by a doctor within the context of a comprehensive medical assessment.

- After we receive your sample, your doctor will typically get the test results within 2 days.

- More than one million people have taken the GeneSight test.

- Many healthcare plans, including Medicare, cover the GeneSight Psychotropic test. There is no cost to the provider to administer the test, and we offer the GeneSight Promise for patients.
We Take Privacy Very Seriously

- We analyze all GeneSight® Psychotropic and GeneSight MTHFR tests at our own accredited lab, so we can ensure the quality and security of your test.

- Your genetic information is private and protected through various federal laws including HIPAA (Health Insurance Portability and Accountability Act) and GINA (Genetic Information Nondiscrimination Act) that ensure the security of your personal and genetic information.

- All samples are destroyed within 60 days of processing.
Questions? Comments? Feedback on this presentation?

Contact Medical Information at: medinfo@myriad.com
(855) 891-9415