Psychiatric Pharmacogenomics: Introduction and Applications

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Current Medication Decision Factors

- Patient Experience
- Adherence
- Adverse Effects
- Illness
- Family History
- Cost

Medication Selection
## Challenges in Clinical Practice

### LACK OF RESPONSE

~50% of patients with depression do not respond to their first treatment\(^1\)

### SIDE EFFECTS

In clinical studies, up to 30% of patients discontinued treatment due to intolerable side effects\(^2,3\)

### NONADHERENCE

Up to 70% of patients receiving prescriptions for antidepressant drugs are nonadherent, with side effects being the most common reason\(^4,5\)

These challenges can lead to symptomatic decline, the need to change medication, and frustration for both the patient and the clinician.

Antidepressant Efficacy

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

<table>
<thead>
<tr>
<th>Step</th>
<th>QIDS-SR16 Response</th>
<th>Treatment Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47%</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>18%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Three Patients

Patient 1
Venlafaxine XR 75 mg qd
No SE
Full remission

Patient 2
Venlafaxine XR 150 mg qd
Severe SE: GI, fatigue, sexual
No response

Patient 3
Venlafaxine XR 300 mg qd
No SE
No response

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Pharmacogenomics Defined

Pharmacogenomics uses information about a person’s genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person.

National Institutes of Health
National Human Genome Research Institute
Personalized Medication Selection Factors
Central Dogma of Genetics

DNA creates RNA, which creates proteins
DNA changes can have profound effects on protein production and function
Four nucleotide base molecules (A, G, T, C) comprise the information in DNA.

- Adenine
- Guanine
- Cytosine
- Thymine

The two bases on the DNA duplex molecule are called base pairs.
Genes and Alleles

A gene is a sequence of DNA that codes for a protein.

An “allele” is the term that refers to the different versions of a gene.

In most cases, we randomly inherit one copy of each gene from each parent.

The combination of alleles (genotype) that we receive creates a certain physical presentation (phenotype).
Pharmacokinetics and Pharmacodynamics

Polymorphisms in pharmacodynamic (PD) genes can affect drug action at its target (e.g., receptor binding).

Polymorphisms in pharmacokinetic (PK) genes (e.g., CYP450) can affect drug blood levels.

Systemic Circulation

Excretion
Key Pharmacogenomic Genes

**GeneSight Psychotropic**

Pharmacokinetic (PK)
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2
- CYP2B6
- CYP3A4

Pharmacodynamic (PD)
- SLC6A4 (serotonin transporter)
- 5HTR2A (serotonin 2A receptor)

**GeneSight Analgesic**

Pharmacokinetic (PK)
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2
- CYP2B6
- CYP3A4

Pharmacodynamic (PD)
- OPRM1 (μ-opioid receptor)

**GeneSight ADHD**

Pharmacokinetic (PK)
- CYP2D6

Pharmacodynamic (PD)
- ADRA2A (α-2A adrenergic receptor)
- COMT (catechol-o-methyltransferase)

**GeneSight MTHFR**

Pharmacokinetic (PK)
- MTHFR (methyltetrahydrofolate reductase)
THE CYP450 System

The CYP450 system is a family of about 57 enzymes responsible for drug metabolism, primarily in the liver. Multiple enzymes may be involved in the metabolism of a given drug.
A highly variable gene with 17 common, clinically relevant polymorphisms.

Located at a site on chromosome 22.

Duplications can occur.
CYP2D6 Expression & Phenotype

*1/*1 Genotype

Extensive Metabolizer Phenotype
CYP2D6 Expression & Phenotype

Chromosome 22

CYP2D6 Gene

*1 Duplication

CYP2D6 Gene

*1 Normal

CYP2D6 Enzyme

*1 Duplication

*1 Normal
CYP2D6 Expression & Phenotype

*1/*5 Genotype

Intermediate Metabolizer Phenotype

*1 Normal
*5 Deletion

CYP2D6 Gene

Chromosome 22

CYP2D6 Enzyme
CYP2D6 Expression & Phenotype

*5/*5 Genotype

Poor Metabolizer Phenotype
How Genetics Can Affect Medication Blood Levels

CYP2D6 Phenotype Frequency*

- **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.

*Phenotype frequency is based on internal Assurex Health data of over 100,000 tested patients.
Paroxetine Plasma Levels by Dose

Paroxetine Plasma Levels by Dose

Three Patients

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Venlafaxine XR 75 mg qd
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No response

CYP2D6 EM
CYP2D6 PM
CYP2D6 UM

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The FDA and Pharmacogenomics

The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts of many of the medications in the GeneSight Psychotropic test:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended Dose/Action</th>
<th>CYP2D6 Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>“The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose.”</td>
<td>CYP2D6 PM</td>
</tr>
<tr>
<td>Citalopram</td>
<td>“The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers.”</td>
<td>CYP2C19 PM</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>“The use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated.”</td>
<td>CYP2D6 IM or PM</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>“The maximum recommended dose of BRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers.”</td>
<td>CYP2D6 PM</td>
</tr>
</tbody>
</table>

The contents of this page have not been endorsed by the FDA and are the sole responsibility of Assurex Health.
Serotonin Transporter (SLC6A4)
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).

The two variants are differentiated by a 44 base pair insertion/deletion.

The short allele results in lower transcription rates, providing less active sites for SSRIs.

The short allele is associated with lower rates of remission following SSRI treatment.
Clinical Utility: GeneSight vs. Standard of Care

Meta-analysis of published literature of the association of 5-HTTLPR with SSRI efficacy in depression – 1435 patients and 15 studies

- Patients with s/s variant had significantly lower remission rates (p<0.0001)
- Patients with s/s and s/l variants had significantly lower response rates (p=0.0002)\(^1\)
- Two other meta-analyses confirmed similar significant associations\(^2,3\)

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Interpreting PGx testing can get complex…

<table>
<thead>
<tr>
<th>Pharmacokinetic Markers</th>
<th>Pharmacodynamic Markers</th>
</tr>
</thead>
<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></td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4</td>
<td></td>
</tr>
<tr>
<td>CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4 + CYP2B6</td>
<td></td>
</tr>
</tbody>
</table>

20,736 Resultant Composite Phenotypes
Integration of Pharmacogenomic Data

Laboratory Analysis of Genotype

Creation of Patient Genetic Profiles

Integration with Psychiatric Pharmacology

Interpretive Report Classification

20,736 Patient Genetic Profiles x 38 Medications = 787,968 Drug Cautions
The Solution: GeneSight Psychotropic
Patient Case Study #1

**Patient Summary**
- 58 yo married woman
- Persistent depression, thyroid problems, insomnia
- Recent life events which contribute to current depressive episode
  - **History:** Difficult childhood (alcoholism and verbal abuse between parents)
  - **Current:** The loss of two of her brothers, a knee replacement, carpal tunnel surgeries and thyroid problems

- Husband works with disability, but she recently lost her job leaving her with only 6 months of insurance coverage remaining

**Patient Exam**
- Patient presents as glum, listless, distracted, disheveled, and appears anxious. Speech, thinking, and physical movement appear slowed by depressed mood. Thought content is depressed. Homicidal ideas or intentions are denied. Vocabulary and fund of knowledge indicate cognitive functioning in the normal range. Insight into problems appears normal. There are no signs of hyperactive or attentional difficulties. **BEHAVIOR:** Patient's behavior in the session was cooperative and attentive with no gross behavioral abnormalities. No signs of withdrawal or intoxication are in evidence.
Patient Case Study #1

**Current Medications**
After years of treatment, no medication has appropriately addressed depression.

She has been started on citalopram and later Luvox, Remeron, Tofranil, and Paxil without a definite improvement.

“Patient needs a Genesight test to identify which medication she may respond to best and has also been referred for therapy.”
### Patient #1 Genotype / Phenotype Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Metabolism Type</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Poor Metabolizer</td>
<td>*4/*4</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Extensive Metabolizer</td>
<td>*1/*17</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Extensive Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Extensive Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Extensive Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Extensive Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Intermediate Response</td>
<td>L/S</td>
</tr>
<tr>
<td>HTR2A</td>
<td>Intermediate Activity</td>
<td>G/A</td>
</tr>
</tbody>
</table>
Patient #1 GeneSight Results

**Antidepressants**

**USE AS DIRECTED**
- desvenlafaxine (Pristiq®)
- levomilnacipran (Fetzima®)
- selegiline (Emsam®)
- vilazodone (Viibryd®)

**USE WITH CAUTION**
- bupropion (Wellbutrin®)
- citalopram (Celexa®)
- escitalopram (Lexapro®)
- sertraline (Zoloft®)
- trazodone (Desyrel®)

**USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING**
- amitriptyline (Elavil®)
- clomipramine (Anafranil®)
- desipramine (Norpramin®)
- doxepin (Sinequan®)
- duloxetine (Cymbalta®)
- fluoxetine (Prozac®)
- fluvoxamine (Luvox®)
- imipramine (Tofranil®)
- mirtazapine (Remeron®)
- nortriptyline (Pamelor®)
- paroxetine (Paxil®)
- venlafaxine (Effexor®)
- vortioxetine (Brintellix®)

**Antipsychotics**

**USE AS DIRECTED**
- aripiprazole (Abilify®)
- haloperidol (Haldol®)
- olanzapine (Zyprexa®)
- quetiapine (Seroquel®)

**USE WITH CAUTION**
- clozapine (Clozaril®)
- clorpheniramine (Phenergan®)

**USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING**
- chlorpromazine (Thorazine®)
- iloperidone (Fanapt®)
- risperidone (Risperdal®)
- thioridazine (Mellaril®)

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[1]: Serum level may be too high, lower doses may be required.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[8]: FDA label identifies a potential gene-drug interaction for this medication.
[9]: Per FDA label, this medication is contraindicated for this genotype.
Clinical Pearls

Patient is a poor metabolizer at CYP2D6 making treatment with medications that utilize this pathway difficult. This includes citalopram, Luvox, Remeron, Tofranil, and Paxil.

Patient carries a short promoter for the SLC6A4 gene, which decreases response to SSRIs. Given this information, a less selective medication or a medication that modulates a different neurotransmitter system altogether may be more efficacious.

Perhaps Effexor or Pristiq would be good options?

Patient has significant metabolic deficiencies for Effexor due to slow metabolism.

CYP2D6

Treatment Decision

Pristiq 50mg PO QPM
Melatonin 10mg PO QPM
“Patient is doing much better. Her family life has improved and she was able to get a new job. She has been following up with a therapist for psychotherapy as part of her treatment plan for recurrent depression. The patient is having a better time understanding her recurrent depression through this therapy and our appointments. The medication changes have allowed her to better manage her condition.”
Questions? Comments?
Feedback on this presentation?

Contact Medical Information at:
medinfo@assurexhealth.com