Dr. Chris Bojrab graduated from Wabash College and then attended Indiana University School of Medicine where he received his M.D. He completed a four-year residency in psychiatry at the Indiana University Medical Center. Dr. Bojrab joined Indiana Health Group, a multidisciplinary mental health practice. Dr. Bojrab is a nationally recognized lecturer on psychopharmacology, sleep disorders, mood and anxiety disorders, and presents over 100 programs each year across the nation and internationally. Dr. Bojrab lives in Indianapolis with his wife, and their three children. His hobbies include digital photography, cooking, computers, and scuba diving.
Disclosure of Relevant Financial Relationships

 Disclosure:
 Dr. Bojrab has served as a member of the speakers’ bureau for the following companies (current positions in **bold**):

**Assurex**
Cephalon
Eli Lilly & Company

**Forest Pharmaceuticals**
Janssen Pharmaceuticals
Jazz Pharmaceuticals
Medical World Conferences
Merck
Neuroscience Education Institute

**Pan-American Labs**
Pfizer

**Sunovion**
Takeda-Lundbeck
Teva
Wyeth
Current State of Genetic Testing in Clinical Practice

Christopher D. Bojrab MD, DFAPA
Board Certified Psychiatrist
President, Indiana Health Group
www.indianahealthgroup.com
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
# Challenges in Clinical Practice

<table>
<thead>
<tr>
<th>LACK OF RESPONSE</th>
<th>~50% of patients with depression do not respond to their first treatment&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDE EFFECTS</td>
<td>In clinical studies, up to 30% of patients discontinued treatment due to intolerable side effects&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>NONADHERENCE</td>
<td>Up to 70% of patients receiving prescriptions for antidepressant drugs are nonadherent, with side effects being the most common reason&lt;sup&gt;4,5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

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Central Dogma of Genetics

DNA creates RNA, which creates proteins.
DNA changes can have profound effects on protein production and function.
DNA

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).
Implications for Family History

CYP2B6 alleles
- *1 normal activity
- *6 reduced activity
- *4 increased activity

*4/*6 Normal
*1/*6 Intermediate

*4/*6 Normal
*1/*6 Intermediate

*1/*4 Increased
*4/*6 Normal
*1/*6 Intermediate

*6/*6 Decreased
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.
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.
CYP2D6 Expression & Phenotype

Chromosome 22

CYP2D6 Gene

*1 Duplication

*1 Normal

*1/*1 with dup Genotype

Ultrarapid Metabolizer Phenotype

CYP2D6 Enzyme

*1 Duplication

*1 Normal
CYP2D6 Expression & Phenotype

* Genotype
*1/*1

* Phenotype
Extensive Metabolizer

CYP2D6 Gene
*1 Normal

CYP2D6 Gene
*1 Normal

CYP2D6 Enzyme
*1 Normal

Chromosome 22
CYP2D6 Expression & Phenotype

*1/*5 Genotype

Intermediate Metabolizer Phenotype

CYP2D6 Enzyme

*1 Normal

*5 Deletion
CYP2D6 Expression & Phenotype

*5/*5 Genotype

Chromosome 22
CYP2D6 Gene
*5 Deletion

CYP2D6 Gene
*5 Deletion

Poor Metabolizer Phenotype

*5 Deletion
CYP2D6 Enzyme
*5 Deletion
CYP450 Metabolizer Phenotypes

**Ultrarapid (UM):** Rapid rate of metabolism

**Extensive (EM):** Normal metabolism

**Intermediate (IM):** Reduced rate of metabolism

**Poor (PM):** Slow rate of metabolism

CYP2D6 Phenotype Frequency

- Extensive (EM): 55%
- Intermediate (IM): 22%
- Ultrarapid (UM): 14%
- Poor (PM): 9%
CYP2D6 and Nortriptyline

Number of functional CYP2D6 genes

Plasma concentration/25 mg dose (nmol/L)

Hours

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>FDA Language</th>
<th>Genotype</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
## CYP450 Genes and Medications

<table>
<thead>
<tr>
<th>Gene</th>
<th>Examples of Some Affected Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>tricyclics, paroxetine, fluoxetine, iloperidone</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>citalopram, fluoxetine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>amitriptyline, sertraline, fluoxetine</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>olanzapine, clozapine, fluvoxamine, duloxetine</td>
</tr>
</tbody>
</table>
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 Outcomes

The Hamm Clinic Study was a prospective, cohort study of 44 adults with a primary diagnosis of a major depressive disorder.* The study compared 8 weeks of treatment guided by GeneSight with unguided treatment as usual (TAU).

**MEAN SYMPTOM IMPROVEMENT AT WEEK 8**

<table>
<thead>
<tr>
<th>Measure</th>
<th>GeneSight (n=22)</th>
<th>TAU (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIDS-C16</td>
<td>31.2%</td>
<td>7.2%</td>
<td>0.002</td>
</tr>
<tr>
<td>HAM-D17</td>
<td>30.8%</td>
<td>18.2%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Reduction in Score from Baseline (%)

*Treatment guided by GeneSight resulted in up to a 4-fold greater improvement in symptoms*

Clinical Outcomes

The La Crosse Study was a prospective, cohort study of 165 subjects with a primary diagnosis of a major depressive disorder. The study compared 8 weeks of treatment guided by GeneSight with unguided TAU.

Treatment guided by GeneSight resulted in up to 100% greater improvement in symptoms

Clinical Outcomes

The Pine Rest Study was a double-blind, randomized controlled trial of 49 subjects with a primary diagnosis of a major depressive disorder. The study compared 10 weeks of treatment guided by GeneSight with unguided TAU.


TAU patients who began the trial on red-category medications showed almost no improvement.
The Pine Rest Study was a double-blind, randomized controlled trial of 49 subjects with a primary diagnosis of a major depressive disorder. The study compared 10 weeks of treatment guided by GeneSight with unguided TAU.

Clinical Outcomes

GeneSight patients who were moved off red-category medications showed the most improvement.

In the Pine Rest study, 30% of patients were taking red category medications at baseline.

Thirty percent of the patients in a typical psychiatric practice are taking red category medications, unbeknownst to their treating clinician.
Catechol-O-methyl Transferase

Catechol-O-methyltransferase (COMT) breaks down both norepinephrine and dopamine in the synapse.

COMT gene has a polymorphism (Val158Met) that results in an amino acid change – methionine (met) for valine (val) at codon 158.

Met/Met homozygotes have 4-5x less COMT activity.

Met/Met carriers showed a reduced rate of response to stimulant medications.


ADHD Pharmacogenomics: ADRA2A

The alpha 2A adrenergic receptor is a receptor in the norepinephrine system.

A SNP in the promoter region (-1291G>C) of this gene has been shown to have an effect on response to methylphenidate and the alpha-2A agonists.
OPRM1 encodes the mu opioid receptor, the main target for many analgesic medications.

Patients who are carriers of the G allele for the A118G SNP show a reduced analgesic response with opioid medications such as morphine, codeine, and oxycodone.\textsuperscript{1}

OPRM1 and Adverse Events

Despite showing reduced analgesic response, OPRM1 G-carriers have not been shown to be protected against respiratory depression.¹

One study showed that, among patients with an acute drug overdose, G-carriers were 5.3 times more likely to experience cardiac or respiratory arrest.²

Other data has shown associations with OPRM1 G carriers and likelihood to become addicted to opiates.³


**OPRM1 and Naltrexone**

In contrast to full μ-opioid agonist therapy (e.g. methadone), OPRM1 G-carriers show improved response to naltrexone in dependent patients compared to wild type.

These findings support the use of OPRM1 to select patients for naltrexone therapy.

The importance of Folate

Folate plays a critical role in the formation of SAMe, an important precursor to neurotransmitter synthesis.¹

Folic acid (synthetic form) and dihydrofolate (dietary form) must be converted to l-methylfolate, the usable form, by methylenetetrahydrofolate reductase, an enzyme encoded by the MTHFR gene.²

The C677T SNP in the MTHFR gene confers reduced enzymatic activity.\textsuperscript{1}

Multiple studies have confirmed lower serum folate levels and higher homocysteine levels in individuals with the T/T or T/C genotype relative to the C/C genotype.\textsuperscript{2-4}

MTHFR

<table>
<thead>
<tr>
<th>Folate Intermediates</th>
<th>MTHFR 677 C/C</th>
<th>NORMAL methylfolate levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate Intermediates</td>
<td>MTHFR 677 T/C</td>
<td>INTERMEDIATE methylfolate levels</td>
</tr>
<tr>
<td>Folate Intermediates</td>
<td>MTHFR 677 T/T</td>
<td>Reduced methylfolate levels</td>
</tr>
</tbody>
</table>
Clinical Implications of MTHFR

Folate deficiency is treatable, with multiple options for folate supplementation:

Supplementation with L-methylfolate (5-MTHF), the active form of folate.

Several recent studies have shown that increasing the intake of folic acid can overcome the effect of reduced MTHFR activity, although this has the potential to mask a Vitamin B12 deficiency.¹⁻³

Questions?