Mood Disorders Perspective
Pharmacogenomics and Depression: Treatment Present and Future

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Department of Psychiatry & Psychology
Director, Mayo Clinic Depression Center
Mayo Clinic

Psychiatry in Medical Settings, February 9-11 2017, Phoenix Arizona
**Disclosures- Mark A. Frye M.D. 2017**

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  - NONE
- **Mayo Clinic**
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David A. Mrazek Memorial Lectures

Mayo Clinic Department of Psychiatry & Psychology
Grand Rounds

National Network of Depression Centers
Annual Meeting

Annual Meeting of the American Psychiatric Association

David A. Mrazek M.D., F.R.C. Psych
1947-2013
Pharmacogenomics & Depression

• Diagnostic Implications
  • Early onset bipolar disorder
  • Bipolar depression

• Treatment Implications
  • Pharmacokinetic genetic variation
    • Cytochrome p450 metabolizing enzymes
  • Pharmacodynamic genetic variation
    • Serotonin transporter

• Pharmacogenomics transforming clinical practice
  • FDA warning label revisions

• Future Directions
  • Decision Support Tools
  • Right 10K
Depression & Non-Precision Medicine

- WHO 2020 projections rank Depression 2nd in DALYs
  - 121 million people worldwide
  - 850,000 suicides annually
- SSRIs have transformed the lives of patients who struggle with depression and anxiety disorders
  - >20 FDA approved antidepressants for major depressive disorder
- Antidepressants 2nd most commonly prescribed drug (13%) in REP
  - peak prevalence rate of 26% in women age 50-64
- Genetic variation may contribute to this differential risk/benefit ratio
- **Precision medicine**
  - beyond large-scale clinical trials evidence
  - potentially reduce toxicity and increase response rates

DALYs=Disability Adjusted Life Years
• Established in 2009
• Co-PIs: Mark Frye and Joanna Biernacka
• DNA matched to a rigorous clinical phenotype to facilitate genomic and other biomarker studies of:
  • disease risk
  • treatment response
• Mayo Clinic in collaboration with Lindner Center of HOPE
  • University of Minnesota
  • Universidad de los Andes, Santiago, Chile
  • Universidad Autónoma de Nuevo Leon, Monterey, Mexico
• Currently N = 2140 (1/5/17)
Primary Aim: Examine association of early-onset bipolar disorder with 8 single nucleotide polymorphisms (SNPs) in 3 genes identified using GWAS (CACNA1C, ANK3, ODZ4)

• Treatment of Early Age Mania (TEAM) cases
• Mayo Clinic Bipolar Biobank cases
  • Early Onset Cases (<19)
  • Late Onset Cases
• Mayo Clinic Biobank controls
## Genetic Risk Score (GRS) Analysis Associated with Early Onset Bipolar Disorder

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>Risk score</th>
<th>OR(^1)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mayo Cases vs. Controls</strong></td>
<td>SC-GRS</td>
<td>1.01</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>OR-GRS</td>
<td>1.10</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>TEAM vs. controls</strong></td>
<td>SC-GRS</td>
<td>1.10</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>OR-GRS</td>
<td>1.58</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Mayo EOCs vs. controls</strong></td>
<td>SC-GRS</td>
<td>1.08</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>OR-GRS</td>
<td>1.77</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>TEAM + Mayo EOCs vs. controls</strong></td>
<td>SC-GRS</td>
<td>1.08</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>OR-GRS</td>
<td>1.74</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: EOC, early-onset cases; LOC, late-onset cases; OR, odds ratio; OR-GRS, odds ratio–weighted genetic risk score; SC-GRS, simple count genetic risk score; TEAM, Treatment of Early Age Mania.

Croarkin et al., J Clin Psychiatry 2017, in press
Proteomic multiplex profiling of 320 proteins utilizing the Myriad RBM Discovery Multi-Analyte Profiling platform™

Platform developed to quantify immune mediators and cytokines
  - increasingly recognized in the underlying neurobiology of mood disorders

Consecutive depression treatment seeking patients (UP n=52, BPI n=46, BPII n=49) and healthy controls (n=141) recruited

Models adjusted for:
  - smoking status, history of illicit drug use, age, BMI, years of education (different by groups)
  - gender, lifetime alcohol use, and fasting status (not different)
  - multiple testing

Frye et al., Translational Psychiatry 2015.
GDF15=Growth Differentiation Factor, HPN=Hepsin, HPX= Hemopexin, MMP7= Matrix Metalloproteinase 7, RBP4=Retinal Binding Globulin 4, TTR= Transthyretin, Frye et al., Translational Psychiatry 2015
### Post-hoc Pairwise Comparison Between Diagnostic Groups

<table>
<thead>
<tr>
<th>Protein</th>
<th>All Groups</th>
<th>BP I, BP II, UP vs Controls</th>
<th>BP I, BP II vs Controls</th>
<th>BP I vs Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>AUC</td>
<td>P</td>
</tr>
<tr>
<td>GDF-15</td>
<td>0.0220</td>
<td>1</td>
<td>0.70</td>
<td>0.0139</td>
</tr>
<tr>
<td>Hemopexin (HPX)</td>
<td>0.0412</td>
<td>1</td>
<td>0.62</td>
<td>1</td>
</tr>
<tr>
<td>Hepsin (HPN)</td>
<td>0.0388</td>
<td>1</td>
<td>0.69</td>
<td>0.0135</td>
</tr>
<tr>
<td>MMP-7</td>
<td>0.0036</td>
<td>0.025</td>
<td>0.66</td>
<td>0.0087</td>
</tr>
<tr>
<td>RBP-4</td>
<td>0.0001</td>
<td>1</td>
<td>0.74</td>
<td>0.5220</td>
</tr>
<tr>
<td>Transthyretin</td>
<td>0.0048</td>
<td>1</td>
<td>0.63</td>
<td>1</td>
</tr>
</tbody>
</table>

- **P** Statistically Significant (after Bonferroni correction)
- **Good Prediction**
- **Fair Prediction**

**Frye et al Translational Psychiatry 2015**
The P450 Drug Metabolizing Enzymes Genes

- One gene for each enzyme
- Extensive variability 2D6 has ~100 polymorphisms
- Variability across ethnic groups
- 4 phenotypes
  - Poor Metabolizer (PM)
  - Intermediate Metabolizer (IM)
  - Extensive Metabolizer (EM) - normal
  - Ultrarapid Metabolizer (URM)
9 exons and 16 SNPs define the most important CYP2D6 alleles

Each SNP is designated by a number reflecting the nucleotide location of the SNP along the sequence of the gene
Pharmacogenomic Testing for Precision Medicine: Analysis of 5 Actionable Pharmacogenomic Genes

Distributions of RIGHT subjects in CYP2D6, CYP2C9, CYP2C19, SLCO1B1*5, and VKORC1 categories.

Ji et al., Journal of Molecular Diagnostics 2016
Case report

A poor metabolizer of both CYP2C19 and CYP2D6 identified by mechanistic pharmacokinetic simulation in a fatal drug poisoning case involving venlafaxine

J. Jornil a,*, T.S. Nielsen a, I. Rosendal a, J. Ahlner b, A.L. Zackrisson b, L.W.T. Boel a, B. Brock a,c

a Aarhus University, Department of Forensic Medicine, Section for Forensic Pathology and Clinical Forensic Medicine & Section for Toxicology and Drug Analysis, Bredstrups gaards vej 100, 8200 Aarhus N, Denmark
b Department of Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine, Artillerigatan 12, SE-587 58, Linköping, Sweden
c Aarhus University Hospital, Department of Clinical Biochemistry, Bredstrups gaards vej 100, 8200 Aarhus N, Denmark

Psychopharmacology

March 2011

Inadvertent Fatal Imipramine Poisoning of a Child:
What Happened to Tommy?

SHELDON H. PRESKORN, MD

The Annals of Pharmacotherapy  •  2003 March, Volume 37

Combination Risperidone and SSRI–Induced Serotonin Syndrome

Shyam D Karki and Gule-Rana Masood

Case Report

Fluoxetine-Related Death in a Child with Cytochrome P-450 2D6 Genetic Deficiency

FLOYD R. SALLEE, M.D., Ph.D., 1 C. LINDSAY DrVANE, Pharm.D., 2 and ROBERT E. FERREL, Pharm.D. 3
Dose & [Plasma] of Venlafaxine by Metabolizer Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>EM, n = 415</th>
<th>PM, n = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(t test)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose, mg</td>
<td>.963</td>
<td>129.08 (68.30)</td>
<td>128.60 (60.47)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>129.75</td>
<td>132.69</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>19.74–339.62</td>
<td>22.97–316.35</td>
</tr>
<tr>
<td>Plasma sample taken, study day, relative to first dose, mean (SD)</td>
<td>.989</td>
<td>41.11 (24.42)</td>
<td>41.16 (23.47)</td>
</tr>
<tr>
<td>ODV concentration, mean (SD), ng/mL</td>
<td>&lt;.001</td>
<td>221.37 (169.32)</td>
<td>109.97 (94.55)</td>
</tr>
<tr>
<td>Venlafaxine concentration, mean (SD), ng/mL</td>
<td>&lt;.001</td>
<td>77.08 (78.54)</td>
<td>276.76 (234.01)</td>
</tr>
<tr>
<td>Total concentration (ODV + venlafaxine), mean (SD), ng/mL</td>
<td>.056</td>
<td>298.44 (232.72)</td>
<td>386.73 (305.85)</td>
</tr>
</tbody>
</table>

Abbreviations: EM = extensive metabolizer, ODV = O-desmethylvenlafaxine, PM = poor metabolizer.

N=464 patients with MDE from 4 ran, db, placebo controlled studies (6-12 wk duration)

2D6 PK Phenotype and Venlafaxine Response

Error bars represent the SD. 

- P value < .02, EM vs PM.
- P value < .01, EM vs PM.
- P value < .001, EM vs placebo.
- P value < .04, PM vs placebo.

Response is defined as ≥ 50% decrease from baseline score.

HDRS remission is defined as total score ≤ 7.

MADRS remission is defined as total score ≤ 12.

Abbreviations: EM = extensive metabolizer, HDRS$_{17}$ = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, PM = poor metabolizer.

Substrates, Inducers, Inhibitors

- **Substrate**: medication processed by enzyme
- **Inducer**: medication which speeds up the enzyme
- **Inhibitor**: medication which slows the enzyme

Courtesy of Dr. Simon Kung
# Relevant Medications: CYP2D6

## Substrate
- Antidepressants:
  - amitriptyline
  - clomipramine
  - venlafaxine
- Antipsychotics:
  - haloperidol
  - risperidone
  - aripiprazole
- Other psychotropics:
  - atomoxetine
  - amphetamine
- Other non-psychotropics:
  - codeine
  - oxycodone
  - dextromethorphan
  - carvediol
  - s-metoprolol

## Inhibitor
- bupropion
- fluoxetine
- paroxetine
- duloxetine
- sertraline
- citalopram
- methadone
- ranitidine

## Inducer
- dexamethasone
- rifampin

- Can make normal metabolizer into slower metabolizer
FDA Pharmacogenomics Revisions

• Carbamazepine and HLA-B*1502 variation associated with Stevens-Johnson's syndrome
  • patients with ancestry across broad areas of Asia
• Tamoxifen-paroxetine/fluoxetine co-therapy
  • CYP2D6 poor metabolizer phenotype reduces metabolic conversion to chemotherapeutically active endoxifen
• Fluoxetine “should be used with caution in patients with conditions that predispose to QT prolongation and ventricular arrhythmia”
  • conditions include 2D6 poor metabolizer and co-administration of 2D6 inhibitors
• Citalopram and QTc prolongation
• Speculation FDA black box warning of acute treatment emergent suicidal ideation and acute antidepressant induced mania

Nassan et al., Mayo Clinic Proceedings 2016
Carbamazepine (CBZ) & Stevens-Johnson Syndrome (SJS)

- Incidence of SJS higher in Chinese than in Caucasians
- Cases N=44 SJS / TEN in Han Chinese in Taiwan
- Controls N=101 CBZ tolerant (3 mos Rx - no AE) and N=93 Healthy volunteers
- Association between CBZ-SJS and HLA
  - B*1502, Cw*0801, A*1101 and DRB1*1202
- HLAB*1502
  - 44/44 CBZ-SJS, 3/101 CBZ tolerant and 8/93 Volunteers

HLA = Human Leukocyte Antigen

Chung et al., Nature 2004
CYP2C19 Variation, Not Dose Associated with QTc Prolongation

- Citalopram dose dependent QTc increase (20 mg: 8.5 msec, 60 mg 18.5 msec)
- FDA Drug Safety Alert(s) Citalopram
- Dose-dependent QTc prolongation
  - Recommendation to not dose > 40 mg/day
  - Revised > 20 mg / day, > 60 years of age, hepatic impairment, and 2C19 poor metabolizer
- Mayo Clinic retrospective cohort design 8/2004-10/2008
  - CYP2C19 EM, IM and PM
  - EMR review of ECG while on citalopram or escitalopram

Howland 2011 J Psychosoc Nurs Ment Health Serv; Kumar et al., 2014 J Psychopharmacology; McKean et al., 2012 Pharmacoepidemiology; Mrazek et al., 2011 Pharmacogenetic Genomics
CYP2C19 Variation, Not Dose Associated with QTc Prolongation

Howland 2011 J Psychosoc Nurs Ment Health Serv; Kumar et al., 2014 J Psychopharmacology; McKean et al., 2012 Pharmacoepidemiology; Mrazek et al., 2011 Pharmacogenetic Genomics
Serotonin Transporter Gene (SLC6A4) on 17q11.2

- **5HTT-LPR**
  - (44 bp insertion/deletion polymorphism in the Promoter Region)

- **“L” Allele**
- **“S” Allele**

- Long/long almost doubles 5HT-T expression (Lesch et al., 1996 Science)

Courtesy of Dr. Gen Shinozaki
Serotonin Transporter Gene Treatment Response: Meta Analyses

• LL genotype, in contrast to SL and SS genotypes, is associated with a higher response rate to SSRI treatment in patients with unipolar or bipolar depression

• LL genotype, in comparison to SL and SS genotypes, is associated with significantly less side effects

Kato and Serretti 2010, Serretti and Kato 2013
Polymorphism of the 5-HT transporter and response to antidepressants: randomised controlled trial†

Glyn Lewis, Jean Mulligan, Nicola Wiles, Philip Cowen, Nick Craddock, Masashi Ikeda, Deteleva Grozeva, Victoria Mason, David Nutt, Deborah Sharp, Debbie Tallon, Laura Thomas, Michael C. O’Donovan and Tim J. Peters

Background
Antidepressants exhibit a variety of pharmacological actions including inhibition of the serotonin and noradrenaline transporters. We wished to investigate whether genetic variation could be used to target or personalise treatment, in a comparison of selective serotonin reuptake inhibitors (SSRIs) with noradrenaline reuptake inhibitors (NARIs).

Aims
To test the hypothesis that patients homozygous for the long (insertion) polymorphism of the serotonin transporter (5-HTTLPR) have an increased response to SSRI antidepressants but not to NARI antidepressants.

Method
In an individually randomised, parallel-group controlled trial, people meeting criteria for a depressive episode who were referred by their general practitioner were randomised to receive either citalopram (an SSRI) or reboxetine (an NARI). Randomisation was by means of random automated system accessed by telephone. The main outcome was depressive symptoms, measured by Beck Depression Inventory (BDI) total score 6 weeks after randomisation. The trial was registered with the International Standard Randomised Controlled Trials Number registry (ISRCTN31345163).

Results
Altogether 298 participants were randomised to receive citalopram and 303 were randomised to reboxetine. At 6 weeks follow-up, complete data were available for 258 participants taking citalopram and 262 taking reboxetine. We found no evidence to support an influence of 5-HTTLPR on outcome following antidepressant treatment. The interaction term for BDI score at 6 weeks was 0.50 (95% CI –2.04 to 3.03, P = 0.70), which indicated that responses to the SSRI and NARI were similar irrespective of 5-HTTLPR genotype.

Conclusions
It is unlikely that the 5-HTTLPR polymorphism alone will be clinically useful in predicting response to antidepressants in people with depression.

Declaration of interest
P.C. has been a paid member of advisory boards of Eli Lilly, Servier, Wyeth and Xyris, and has been a paid lecturer for Eli Lilly, Servier and GlaxoSmithKline. He has provided expert advice for solicitors representing GlaxoSmithKline. D.N. has acted as consultant and speaker for both Lundbeck and Pfizer.

Table 4 Percentage of patients in remission at 6 weeks according to medication and 5-HTTLPR genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Citalopram group</th>
<th>Reboxetine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>l/l</td>
<td>24.1 (15.1–34.0)</td>
<td>25.3 (17.1–35.0)</td>
</tr>
<tr>
<td>l/s, s/s</td>
<td>22.4 (16.5–29.2)</td>
<td>20.9 (14.9–27.9)</td>
</tr>
</tbody>
</table>

l, long; s, short.
Bipolar Disorder — A Focus on Depression

Mark A. Frye, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

A 26-year-old businesswoman seeks evaluation for a pattern of “hibernating away” each winter; this pattern began when she was in high school. Her current symptoms include excessive sleeping, a 20-lb (9-kg) weight gain related to an increased intake of sweets and excessive alcohol use, anhedonia, lack of motivation, negative ruminations, and decreased productivity at work. She reports a history of several-week periods in college when she had less need for sleep, with associated increases in mood, energy, and libido. During the last episode, she exceeded her credit-card limit and was evaluated at an emergency department for alcohol intoxication. How should she be evaluated and treated?
Risk Factors for Switch

- Mixed Depression
- Tricyclic antidepressants (TCA) vs Venlafaxine
- History of antidepressant-induced mania (AIM)
- Absence of Antimanic Mood Stabilizer
  - First 3 months associated with greatest liability
- Low thyroid stimulating hormone (with TCAs)
- Polymorphism (s/s or s/l) at 5-HTTLPR
- Hyperthymic temperament
- Comorbid alcoholism
- Female gender and comorbid anxiety disorder
- Age (peripubertal > adolescents)
- BP I > BP II
Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (BP)

SLC6A4 polymorphism & Antidepressant Induced Mania
SLC6A4 S Allele and AIM: Meta-Analysis Results

Meta-analysis marginally significant evidence of association between S allele and AIM+ (p=0.059)
Genesight® Psychotropic

• Decision support tool to help clinicians make recommendations based on PK/PD genetic variation

• 22 antidepressants
  • 6 SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
  • 4 SNRIs, (desvenlafaxine, duloxetine, venlafaxine, levomilnacipran)
  • 6 TCAs (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline)
  • 5 atypicals (bupropion, trazodone, vilazodone, vortioxetine, mirtazapine)
  • 1 MAOI (selegiline)

• 16 antipsychotics
  • 5 typical (chlorpromazine, haloperidol, perphenazine, thioridazine, thiothixene)
  • 11 atypical (aripiprazole, asenapine, clozapine, fluphenazine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)

• 8 ADHD medications
  • 5 stimulants (amphetamine salts, methylphenidate, dexamphetamine, dextroamphetamine, and lisdexamfetamine), 1 SNRI (atomoxetine)
  • 2 alpha-2 adrenergic agonists (clonidine, and guanfacine)
### Commercially Available Pharmacokinetic (PK) & Pharmacodynamic (PD) Platforms

<table>
<thead>
<tr>
<th>Genosight Psychotropic Results</th>
<th>Assurex Psychotropic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2D6</strong> Poor Metabolizer</td>
<td><em>4</em> of 4</td>
</tr>
<tr>
<td>CY2D6*4: This allele produces no enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>Comment: This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.</td>
<td></td>
</tr>
<tr>
<td><strong>CYP2C19</strong> Intermediate Metabolizer</td>
<td><em>2</em> of 2</td>
</tr>
<tr>
<td>CY2C19*1: This allele produces normal enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>CY2C19*2: This allele produces no enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>Comment: This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.</td>
<td></td>
</tr>
<tr>
<td><strong>CYP2C9</strong> Intermediate Metabolizer</td>
<td><em>2</em> of 2</td>
</tr>
<tr>
<td>CY2C9*1: This allele produces normal enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>CY2C9*2: This allele produces reduced enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>Comment: This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.</td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A4</strong> Extensive Metabolizer</td>
<td><em>4</em> of 1</td>
</tr>
<tr>
<td>CY3A4*1: This allele produces normal enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>CY3A4*2: This allele produces no enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>Comment: This genotype is most consistent with the extensive metabolizer (normal) phenotype.</td>
<td></td>
</tr>
<tr>
<td><strong>CYP2B6</strong> Extensive Metabolizer</td>
<td><em>1</em> of 1</td>
</tr>
<tr>
<td>CY2B6*1: This allele produces normal enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>CY2B6*2: This allele produces no enzyme activity.</td>
<td></td>
</tr>
<tr>
<td>Comment: This genotype is most consistent with the extensive metabolizer (normal) phenotype.</td>
<td></td>
</tr>
<tr>
<td><strong>CYP1A2</strong> -2467T -&gt; DELT/T-DELT</td>
<td></td>
</tr>
<tr>
<td>This genotype is most consistent with the extensive metabolizer (normal) phenotype.</td>
<td></td>
</tr>
<tr>
<td><strong>SLC6A4</strong> Reduced Response</td>
<td>S/S</td>
</tr>
<tr>
<td>This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the long promoter. This patient may experience a delayed response with selective serotonin reuptake inhibitors, or may benefit from non-selective antidepressants.</td>
<td></td>
</tr>
<tr>
<td><strong>HTR2A</strong> Reduced Activity</td>
<td>G/G</td>
</tr>
<tr>
<td>This individual is homozygous variant for the G allele of the 1-1080 variant polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with selective serotonin reuptake inhibitors.</td>
<td></td>
</tr>
</tbody>
</table>

**FOUND ISSUES**

- **NO ISSUE FOUND**
  - Use as directed for Samantha

- **CAUTION: ISSUE FOUND**
  - Medications may not work for Samantha

- **URGENT: ISSUE FOUND**
  - Medications may not work or cause serious issues for Samantha

**DRUG NAMES**

- amitriptyline (Brand name)
- aripiprazole (Brand name)
- clomipramine (Brand name)
- doxepin (Brand name)
- flecainide (Brand name)
- fluorouracil (Brand name)
- hormonal contraceptives for systemic use (Brand name)

**Assurex Health, Chromocare, PGxOne Plus – Admera Health, Quest Diagnostics, Genele, Idgenetix, Cyprotex, TrimGen**
Genesight vs TAU Baseline Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Mean baseline HAM-D17 score</th>
<th>SEM</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pine Rest</td>
<td>TAU</td>
<td>21.1</td>
<td>0.83</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>GeneSight</td>
<td>21.6</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Hamm</td>
<td>TAU</td>
<td>18.4</td>
<td>1.10</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>GeneSight</td>
<td>20.6</td>
<td>1.22</td>
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<tr>
<td>La Crosse</td>
<td>TAU</td>
<td>22.5</td>
<td>0.49</td>
<td>0.45</td>
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<td></td>
<td>GeneSight</td>
<td>23.0</td>
<td>0.49</td>
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<tr>
<td>Pooled</td>
<td>TAU</td>
<td>21.5</td>
<td>0.41</td>
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<tr>
<td></td>
<td>GeneSight</td>
<td>22.4</td>
<td>0.42</td>
<td></td>
</tr>
</tbody>
</table>

In none of the studies, nor in the pool of the three studies, did these baseline values differ between the two groups.
Response (≥50% decrease from baseline in HAM-D17 score)
Increased OR = 2.26 for achieving a clinical response (p = 0.004) and a greater RB of 1.71-fold (p = 0.01) for subjects in the GeneSight groups as compared to those in the TAU groups. ORs and RBs are reported as the odds and likelihood, respectively, of subjects in the GeneSight group achieving a clinical response as compared to the TAU group. Each pooled OR, RB, and 95% CI, p value, and z value was obtained from random effects models via meta-analysis.

Mayo Clinic Depression Center
Treatment Study Timeline

- Screening Visit
- Baseline Visit 3-5 days later
- 2-Week Visit
- 4-Week Visit
- 8-Week Visit
  - Patient gets results

8-Week Study Trial
Future Directions

• Duke /Emory /Mayo  Subphenotypes of Depression
  • Comprehensive rating scales too heterogenous to probe pharmacogenomics drug response
  • core depression, neurovegetative melancholia, negative valence, positive valence, Shafer anxiety, somatization, and Rush 5.

• Mayo RIGHT 10K Project Center for Individualized Medicine
  • Next Generation Sequencing PGRN-SEQv2 (64 genes)
  • 10,000 individuals from Mayo Community Biobank
  • Genotypes deposited into the EMR which will trigger clinical decision support (CDS) rules
    • ~20 genes, 265 alleles, 300-400 drugs

• Electronic Decision Support Tools
Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine

Malik Nassan, MBBS; Wayne T. Nicholson, MD, PharmD; Michelle A. Elliott, MD; Carolyn R. Rohrer Vitek, MS; John L. Black, MD; and Mark A. Frye, MD

Order or prescription for fluoxetine, paroxetine, citalopram, escitalopram, or venlafaxine

Genetic testing completed?

No

No recommendation for testing

Yes

Phenotypes without alert:
Ultrarapid
Extensive to ultrarapid
Intermediate to ultrarapid
Intermediate
Extensive
Intermediate to extensive

Received alert?

No

Yes

Phenotypes with alert:
Poor
Poor to intermediate

Consider alternative medication
Pharmacogenomic Targets Conclusion

• BP Diagnostics (genomic and proteomic) need replication
  • algorithm to facilitate right diagnosis at earliest time point
• p450 cytochrome genetic variation alters enzyme activity that impact side effects & response
• Non-normal variation in drug metabolizing enzymes (poor/ultra rapid) do not entirely explain side effects /non-response
• Pharmacokinetics does not address pharmacodynamics
  • serotonin transporter (L allele) associated with higher/lower rate of response/side effects respectively
• Early signs of practice transformation
  • FDA warning labels
  • EMR interface clinical decision support (CDS) rules
Patient expectations need to be managed
Funding for the bipolar genomics work was provided by the Marriott Foundation.

Thank you to our bipolar patients and their families who have contributed to the development and richness of this resource.