Genomind and
The Genecept Assay®
To improve the lives of patients with mental illness by bringing innovative technologies to clinical care
Scientific Advisory Board

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## Treatment Resistance in Psychiatry

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Initial Remission Rate</th>
<th>Treatment Resistant/Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (MDD)¹</td>
<td>30-37% (STAR-D)</td>
<td>30% treatment resistant following 4 treatments</td>
</tr>
<tr>
<td>Bipolar Disorder (BD)²</td>
<td>24-77% (STEP-BD)</td>
<td>50-70% relapse rates</td>
</tr>
<tr>
<td>Schizophrenia³,⁴</td>
<td>16-44% (CATIE)</td>
<td>Up to 74% discontinue medications due to lack of efficacy or poor side effects after 18 months</td>
</tr>
<tr>
<td>Anxiety (GAD)⁵,⁶</td>
<td>12-60%</td>
<td>Recurrence in up to 50%</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder (OCD)⁷,⁸</td>
<td>25-71%</td>
<td>Up to 80% in 10 year follow-up</td>
</tr>
</tbody>
</table>

30-80% of psychiatric patients have unresolved symptoms. Many have abandoned drug therapies due to inefficacy or side effects.

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1) STAR-D: NIMH
2) STEP-BD: NIMH
3) Perry et al. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ 1999;318:149, dx.doi.org/10.1136/bmj.318.7177.149
4) CATIE:NIMH
6) Yonkers et al. Phenomenology and course of generalised anxiety disorder. 10.1192/bjp.168.3.308 March 1996
8) Deborah Cowley, MD . Long-Term Outcomes Are Poor in Obsessive-Compulsive Disorder. reviewing Bloch MH et al. Depress Anxiety 2013 Mar 26
Treatment Resistance: Depression

What Are Biomarkers?

Gene Based:
- Single Nucleotide Polymorphisms (SNPs)

Epigenetics:
- Methylation
- Acetylation

Gene Expression and Proteins

Brain Imaging

Strimbu and Tavel 2010.
## 18 Genes Analyzed

<table>
<thead>
<tr>
<th>Gene</th>
<th>Physiological Role</th>
<th>Impact of Mutation</th>
<th>Treatment Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin Transporter (SLC6A4)</td>
<td>Protein responsible for reuptake of serotonin from the synapse</td>
<td>Inhibition of this protein by SSRIs, which may lead to increased risk for non-response/side effects</td>
<td>Use caution with SSRIs; atypical antidepressants or SNRIs may be used if clinically indicated</td>
</tr>
<tr>
<td>Calcium Channel (CACNA1C)</td>
<td>A subunit of the calcium channel which mediates excitatory signaling</td>
<td>Associated with conditions characterized by mood instability/ability</td>
<td>Atypical antipsychotics, mood stabilizers, and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated</td>
</tr>
<tr>
<td>Sodium Channel (ANK3)</td>
<td>Protein that plays a role in sodium channel function and regulation of excitatory signaling</td>
<td>Associated with conditions characterized by mood instability/ability</td>
<td>Mood stabilizers and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated</td>
</tr>
<tr>
<td>Serotonin Receptor 2C (5HT2C)</td>
<td>Receptor involved in regulation of satiety</td>
<td>Blocked by atypical antipsychotics, resulting in metabolic side effects</td>
<td>Use caution with atypical antipsychotics; inositol may be used to mitigate risk for weight gain if clinically indicated</td>
</tr>
<tr>
<td>Melanocortin 4 Receptor (MC4R)</td>
<td>Receptor that plays a role in the control of food intake</td>
<td>Increased risk for weight gain and higher BMI, which is exacerbated by atypical antipsychotics</td>
<td>Use caution with atypical antipsychotics</td>
</tr>
<tr>
<td>Dopamine 2 Receptor (DRD2)</td>
<td>Receptor affected by dopamine in the brain</td>
<td>Blocked by antipsychotic medications and is associated with risk for non-response/side effects</td>
<td>Use caution with antipsychotics</td>
</tr>
<tr>
<td>Catechol-O-Methyltransferase (COMT)</td>
<td>Enzyme primarily responsible for the degradation of dopamine in the frontal lobes of the brain</td>
<td>Altered dopamine states can have emotional/behavioral effects and impact response to dopaminergic agents</td>
<td>Dopaminergic agents or TMS may be used if clinically indicated for Val/Val patients</td>
</tr>
<tr>
<td>Alpha-2A Adrenergic Receptor (ADRA2A)</td>
<td>Receptor involved in neurotransmitter release</td>
<td>Associated with improved response to stimulant agents</td>
<td>Use caution with dopaminergic agents in Met/Met patients</td>
</tr>
<tr>
<td>Methylene Tetrahydrofolate Reductase (MTHFR)</td>
<td>Predominant enzyme that converts folic acid/folate to its active form (methylfolate) needed for synthesis of serotonin, dopamine, and norepinephrine</td>
<td>Associated with varied activity and conversion of folic acid/folate to methylfolate</td>
<td>Supplementation with L-methylfolate may be used if clinically indicated</td>
</tr>
<tr>
<td>Brain-derived Neurotrophic Factor (BDNF)</td>
<td>Important for proper neuronal development and neural plasticity</td>
<td>Impaired BDNF secretion, which may be associated with altered SSRI response in Caucasians</td>
<td>Increased physical activity/exercise may be beneficial for Met carriers if clinically indicated</td>
</tr>
<tr>
<td>µ-Opioid Receptor (OPRM1)</td>
<td>Opioid receptor affected by natural and synthetic compounds</td>
<td>Activated by opioids and associated with varied analgesic response, dosage, and abuse/addiction risk</td>
<td>Use caution with opioids; non-opioid analgesics may be used if clinically indicated</td>
</tr>
<tr>
<td>Glutamate Receptor (GRK1)</td>
<td>An excitatory neurotransmitter receptor in the brain</td>
<td>Associated with response to topiramate for alcohol abuse</td>
<td>Topiramate may be used for treatment of alcohol abuse if clinically indicated</td>
</tr>
<tr>
<td>CYP1A2, CYP2B6, CYP2C9</td>
<td>Enzymes that metabolize medications in the liver</td>
<td>Large number of psychiatric medications are metabolized by CYP450s</td>
<td>Dose adjustment (an increase or decrease) may be required</td>
</tr>
<tr>
<td>CYP2C19, CYP2D8, CYP3A4/5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

= newly added to the Genecept Assay, January 2016.

Genetics 101
Nature vs. Nurture

- In psychiatry we do a good job of determining what environmental factors have contributed to a particular disorder.
- Until now, we have not had access to a large component of our phenotype.....genetic factors

GENES + Environment = Phenotype

GENECEPT ASSAY + Patient History = Personalized Treatment
Gene/Environment Interaction

![Graph showing the gene-environment interaction between methylenetetrahydrofolate reductase (MTHFR) genotype and traumatic childhood events (TCEs) on depressive symptoms in 665 individuals from the general population.](image)

**Figure 2** The gene-environment interaction between methylenetetrahydrofolate reductase (MTHFR) genotype and traumatic childhood events (TCEs) on depressive symptoms in 665 individuals from the general population ($P = 0.0027$). 0, T/T genotype; 1, C/T genotype; and 2, C/C genotype.
Gene variants associated with altered liver enzyme metabolism activity may lead to *side effects and toxicity*

<table>
<thead>
<tr>
<th>PM</th>
<th>Poor metabolizers or inhibitors of P450 may have increased drug serum levels and adverse events.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>Intermediate metabolizers or inhibitors of P450 may have increased drug serum levels and adverse events.</td>
</tr>
<tr>
<td>EM</td>
<td>Extensive metabolizers metabolize substrates normally.</td>
</tr>
<tr>
<td>UM</td>
<td>Ultra-rapid metabolizers or inducers of P450 may have reduced drug serum levels and poor efficacy.</td>
</tr>
</tbody>
</table>

FDA warning (Aug 2011): Citalopram **maximum dose of 20mg in CYP2C19 poor metabolizers** and those receiving CYP2C19 inhibitors
Major Psychotropic Substrates

**Antidepressants:**
- Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Mirtazapine, Paroxetine, TCA's, Venlafaxine*, Vortioxetine

**Antipsychotics:**
- Aripiprazole, Brexpiprazole, Clozapine, Iloperidone, Olanzapine, Risperidone, Chlorpromazine, Fluphenazine, Haloperidol, Perphenazine, Pimozide, Thioridazine

**Stimulants/NRI:**
- Amphetamine, Dextro-amphetamine, Methamphetamine, Atomoxetine

**Pain:**
- Codeine*, Hydrocodone*, Oxycodone, Tramadol

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**Antidepressants:**
- Citalopram, Escitalopram, TCA's, Venlafaxine*

**Pain:**
- Carisoprodol

**Anxiolytic:**
- Diazepam

**Pain:**
- Caisoprodol

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**Antidepressants:**
- Citalopram, Levomilnacipran, Mirtazapine, Trazodone, Trimipramine, Vilazodone

**Mood Stabilizer:**
- Carbamazepine

**Miscellaneous stimulants:**
- Armodafinil, Guanfacine, Modafinil

**Anxiolytic:**
- Alprazolam, Buspirone, Chlordiazepoxide, Clonazepam, Diazepam

**Pain:**
- Alfentanil, Fentanyl, Methadone, Oxycodone, Tramadol

**Antipsychotics:**
- Aripiprazole, Brexpiprazole, Cariprazine, Clozapine, Lurasidone, Quetiapine, Haloperidol, Pimozide

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*pro-drug conversion

Major Psychotropic Substrates

CYP1A2
- Antidepressants: Clomipramine, Duloxetine, Fluvoxamine, Mirtazapine
- Antipsychotics: Asenapine, Clozapine, Olanzapine, Thiothixene, Trifluoperazine
- Pain: Cyclobenzaprine, Tizanidine

CYP2B6
- Antidepressants: Bupropion, Selegiline
- Pain: Methadone

CYP2C9
- Antidepressants: Fluoxetine
- Pain: Celecoxib, Diclofenac, Flurbiprofen, Meloxicam, Piroxicam

Serotonin Transporter (SLC6A4)

- SLC6A4 is reported as L(A) (normal) or L(G) or S(risk)
- Patients carrying the S or L(G) allele are at higher risk for side effects and lack of response to SSRIs

Clinical Impact:
- Caution with SSRIs
- Therapeutic Options: SNRIs and Atypical Antidepressants
Ion Channels in the Brain and Psychiatric Disorders

Activating GLU receptors leads to depolarization as Na⁺ enters the cell. Depolarization opens Ca⁺⁺ channels which are responsible for neurotransmitter release.

- Homozygotes of the ANK3 ‘T’ allele or CACNA1C ‘A’ allele are at higher risk of altered neuronal signaling.
- **Clinical Impact**: therapeutic options include agents that reduce neuronal signaling such as mood stabilizers, atypical antipsychotics, omega 3 fatty acids.

Ferreira et al., 2008
The regulation of feeding behavior and energy balance is highly complex and controlled mainly in the hypothalamus.

- Serotonin signaling regulates satiety through activation of 5HT2C receptors.
- MC4R is activated by anorectic peptides to induce satiety and inhibited by orectic peptides to inhibit satiety.

**Anorectic Peptides** (α-MSH, CNTF, CRH)

**Orectic Peptides** (NPY, AgRP, Ghrelin)

- Decreased food intake
- Increased energy expenditure
- Increased food intake
- Decreased energy expenditure

5HT2C and MC4R Genetic Variations Affect Metabolic Risk

**Mutation**

- 5HT2CC allele is wildtype, however T mutation confers protective affect against weight gain
- MC4RA allele may increase risk for weight gain and higher BMI

**Clinical Impact**

- Atypical antipsychotics exacerbate the risk for weight gain for A allele carriers
- Use caution with atypical antipsychotics
  - **High risk medications**: clozapine and olanzapine
  - **Medium risk medications**: aripiprazole; iloperidone; paliperidone; quetiapine; risperidone
  - **Low risk medications**: asenapine; cariprazine; brexipiprazole; lurasidone; ziprasidone

Dopamine Receptor (DRD2)

- Antipsychotic clinical efficacy is highly correlated with the binding affinity to the Dopamine 2 Receptor

- Deletions (DEL) in the dopamine receptor gene can alter binding affinity and receptor density leading to poorer outcomes with atypical and typical antipsychotics.

- Indicates that antipsychotics are less likely to be effective and more likely to cause side effects.

Clinical Impact: Use with caution or alternative agent

Zang et al 2010
Catechol-o-methyltransferase (COMT)

- COMT is found in the prefrontal cortex; responsible for dopamine degradation

<table>
<thead>
<tr>
<th>COMT Activity</th>
<th>DA Levels</th>
<th>Clinical Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (Val/Val)</td>
<td>Low</td>
<td>• Impaired Executive Function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Superior response with Stimulants</td>
</tr>
<tr>
<td>Low (Met/Met)</td>
<td>High</td>
<td>• Superior Executive Function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Caution with Stimulants</td>
</tr>
</tbody>
</table>

Folate Metabolism

- Depending on the different combinations of C677T and A1298C alleles, total conversion rates of folic acid range from 100% to <30%
  - C677T; T = 35% reduction in activity
  - A1298C; C = 20% reduction in activity
MTHFR Polymorphism

Clinical Utility

- L-methylfolate supplementation may be relevant in patients with the T allele

Papakostas et al 2012; Ginsberg et al 2011; Wade et al 2014; Papakostas et al 2014;
Brain-derived Neurotrophic Factor (BDNF)

**Mutation**

- rs6265 (Val66Met) – Met linked to impaired cellular secretion and transport, which may indirectly affect expression levels

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Martinez-Levy GA, Cruz-Fuentes CS 2014; Hosand et al 2014
BDNF and Physical Activity

Clinical Impact:
- Greater levels of physical activity can offset the deleterious effect of Met allele on working memory (Erickson, 2013)
- Exercise has been linked to improved cognition, working memory, and higher BDNF levels

Potential Clinical Impact:
- Val/Met and Met/Met genotypes may be at risk for depression symptoms, impaired working memory, and altered stress response
- Studies have shown that Caucasian Met carriers have poorer response to SSRIs, while Val/Val patients may have superior response to SSRIs/TMS (Colle, 2015)
  - Larger studies and replication studies need to be conducted to confirm this association

Erickson et al 2013; Colle et al 2015
**μ-Opioid Receptor (OPRM1)**

**Mutation**
- The G allele is associated with decreased response to opioids and increased risk for addiction

**Clinical Impact**
- Clinicians may increase dose for G allele carriers, however these patients are at risk for substance abuse
- Non-opioid analgesics may be recommended for G allele carriers

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype frequency, demand and consumed morphine dose in milligrams for the patients who received patient-controlled analgesia alone.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Genotype frequency (%)</th>
<th>Demand in first 24 h</th>
<th>Demand in second 24 h</th>
<th>Demand in first 48 h</th>
<th>Dose in first 24 h</th>
<th>Dose in first 48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>62</td>
<td>24.3 (15.4)</td>
<td>9.5 (9.4)</td>
<td>39.0 (24.7)</td>
<td>16.0 (8.0)</td>
<td>25.3 (15.5)</td>
</tr>
<tr>
<td>GG</td>
<td>11</td>
<td>36.1 (15.2)</td>
<td>18.3 (14.9)</td>
<td>57.8 (24.7)</td>
<td>22.3 (10.0)</td>
<td>40.4 (22.1)</td>
</tr>
</tbody>
</table>

Data Behind the Genecept Assay
- S/S genotype were poor responders to SSRI medications
- L carriers had 58% better response rates
- Sicard et al., 2010
- Carriers of the C allele are more likely to gain weight taking atypical antipsychotics
Zhang et al., 2010

Patients with the DRD2 deletion are less likely to respond to antipsychotics
Hamidovic et al. 2010

Amphetamine improves the cognitive performance of Val/Val patients only

Figure 2.
Mean Area Under the Curve±SEM of subjects' performance on the Digit Symbol Substitution Test according to COMT val158met genotype. The groups did not differ significantly on the placebo session, but D-amphetamine 10 mg (***p<0.001) and D-amphetamine 20 mg (***p<0.001) improved performance in the val/val carriers (N=36). D-Amphetamine (20 mg) improved performance in the val/met (N=72) carriers (***p<0.01) whereas the drug did not change performance in the met/met carriers (N=53).
MTHFR

Papakostas et al., 2012

Methylfolate is a beneficial augmentation to SSRIs

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**FIGURE 1. Pooled Response Rates in Two Trials of L-Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression**

<table>
<thead>
<tr>
<th>Trial 1 (7.5 mg/day for 30 days) (N=148)</th>
<th>Trial 2 (15 mg/day for 30 days) (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI plus MTHF</td>
<td>SSRI monotherapy</td>
</tr>
<tr>
<td>18.3%</td>
<td>18.8%</td>
</tr>
<tr>
<td>32.3%</td>
<td>14.6%</td>
</tr>
</tbody>
</table>

*Response was defined as a reduction of ≥50% in Hamilton Depression Rating Scale score during treatment or a final score of ≤7. Significant difference between groups in trial 2 (p=0.04). The pooled analysis was conducted as described in Fava et al. (25).
3-month prospective study with 685 patients

- 70% with primary mood disorder (43% with MDD, 17% Bipolar, 10% other) and 29% with primary Anxiety disorder
- Treatment-resistant population → 69% of patients had ≥ 2 previous failed treatment trials with a mean of 3.3

Specific aims:

- Determine the effectiveness of the Geneceopt Assay based on clinician-rated and patient-rated measures; and
- Assess its influence on clinician treatment decisions
Clinician Reported Outcomes

91% of treatment resistant patients (i.e. those with ≥ 2 previous adequate treatment trials) showed clinically-measurable improvement, with 64% of treatment resistant patients demonstrating significant clinical improvement (deemed as 1 - “very much improved” or 2 - “much improved”).
Response Rates Exceed Seminal STAR*D Trial

Response Rates by Treatment Trials\(^{(1,2)}\)

<table>
<thead>
<tr>
<th>Level</th>
<th>STAR*D</th>
<th>Genecept- Clinician Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N=3,671/93)</td>
<td>49%</td>
<td>59%</td>
</tr>
<tr>
<td>2 (N=1,439/103)</td>
<td>29%</td>
<td>55%</td>
</tr>
<tr>
<td>3 (N=390/94)</td>
<td>17%</td>
<td>69%</td>
</tr>
<tr>
<td>4 (N=123/79)</td>
<td>16%</td>
<td>66%</td>
</tr>
<tr>
<td>5 + Failed Trials (N=N/A/75)</td>
<td>0%</td>
<td>75%</td>
</tr>
<tr>
<td>4 Failed Trials (N=N/A/75)</td>
<td>4%</td>
<td>56%</td>
</tr>
</tbody>
</table>

- Response rates with Genecept Assay™ were comparable for patients, regardless of number of failed treatment trials
- An average of 63% of patients across all levels of treatment resistance showed a clinically significant response

1) Levels indicate either stages of treatment in STAR*D or number of previously failed adequate treatment trials, with level 1 indicating zero previous treatment trials
2) Response measured by ≥ 50% reduction in QIDS-SR16 (STAR*D) or CGI-I of 1 or 2 (Genecept™-Clinician Reported)

Brennan et al 2014.
Patient-reported depression, anxiety and medication side effect measures decreased substantially with Genecept-guided treatment, while quality-of-life substantially improved.
The Genecept Assay – How it Works

*Results of the test, combined with expert clinical consultations, enable better patient responses to treatment.*

1. Patients provide cheek swab via a collection kit supplied by Genomind
2. Prepaid overnight shipping packet and barcoded requisition form provided so patient sample can be sent securely to Genomind’s lab
3. Genomind’s CLIA-certified lab performs test with 3-5 day turnaround time
4. Online analytical report delivered to clinician to inform treatment decisions
5. Genomind-certified physicians and PharmD’s available to discuss results with treating clinicians via telephonic consult
The Value of Genomind’s Clinical Consultation

Personalized access to consultations with Genomind certified physicians, Ph.D.’s and Pharm.D.’s, in conjunction with every patient report in a timely manner

Creates a significant connection between the patient, their clinical history, their genetic results, and the treating clinician

Enhances education of biomarkers and translation of genetic results into potential treatment strategies

Can be leveraged for the clinician’s family consultations and program discharge planning

Case Study

- 42 y/o male, fully employed with 2 children
- Chronic diagnosis of MDD for more than 20 years
- Presents with refractory depression, thoughts of sadness and suicidal ideation and mood swings
- Fluoxetine and escitalopram led to minimal improvement of symptoms, d/c due to inefficacy and/or side effects
Case Study

Currently taking no meds, but admits to periodic ETOH binge use

- What would your treatment choice be?
  - Sertraline
  - Duloxetine
  - Bupropion
  - Mood stabilizer
  - Methylfolate
### RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

<table>
<thead>
<tr>
<th>GENE RESULT</th>
<th>THERAPEUTIC IMPLICATIONS</th>
<th>INTERACTION</th>
<th>CLINICAL IMPACT</th>
</tr>
</thead>
</table>
| Serotonin Transporter (SLC6A4) S/S [High risk of non-response] | SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake  
- SSRIs act by blocking this transporter to produce a therapeutic response  
- Higher risk of poor response, slow response or intolerance to SSRIs; potential increased risk for PTSD and reduced stress resilience  
- Therapeutic options such as atypical antidepressants or SNRIs may be used as clinically appropriate | ! | Therapeutic options; atypical antidepressants or SNRIs may be used if clinically indicated |
| Calcium Channel (CACNA1C) A/A [Highest risk of altered neuronal signaling] | CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain  
- Abnormal calcium signaling may be clinically associated with conditions characterized by mood instability or liability | ! | Therapeutic options; atypical antipsychotics, mood stabilizers and/or omega-3 fatty acids may be used if clinically indicated |
| Melanocortin 4 Receptor (MC4R) A/A [High weight gain risk] | MC4R is a receptor that plays a central role in the control of food intake  
- Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics  
- High risk: Clozapine; Olanzapine;  
- Medium risk: Aripiprazole, Iloperidone, Paliperidone, Quetiapine, Risperidone  
- Lower risk: Asecapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone | ! | Use caution with atypical antipsychotics |
| Methyltetrahydrofolate Reductase (MTHFR) T/T | MTHFR is an enzyme responsible for the conversion of folate acid to methylfolate which is a precursor needed for serotonin, norepinephrine and dopamine synthesis  
- Risk for reduced MTHFR enzyme activity and reduced methylfolate production  
- Folic acid-based supplementation of SSRIs and SNRIs show superior symptom reduction and medication adherence compared to SSRIs/SNRIs alone in Major Depressive Disorder | ! | Higher intake of folic acid based interventions may be required |
| Brain-derived Neurotrophic Factor (BDNF) Met/Met | BDNF is a protein involved in neuronal development and neural plasticity  
- Potential risk for increased depression symptoms, impaired working memory, and altered stress response  
- Studies have shown that Met carriers may have less satisfactory response to SSRIs in Caucasians, but not Asians, however larger studies need to be conducted to confirm these findings  
- Exercise has been linked to improvements in cognition, and recent studies show that Met allele carriers may demonstrate enhanced effects of exercise on working memory compared to Val/Val patients | ! | Therapeutic options; increased levels of physical activity/exercise if clinically appropriate |

## Patient Results

**Data on file. Genomind 2016.**

<table>
<thead>
<tr>
<th>GENE RESULT</th>
<th>THERAPEUTIC IMPLICATIONS</th>
<th>INTERACTION</th>
<th>CLINICAL IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Channel (ANK3)</td>
<td>ANK3 is a protein that plays a role in sodium ion channel function and is involved in</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>(C/C)</td>
<td>excitatory signaling in the brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• This genotype confers normal activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin Receptor 2C</td>
<td>5HT2C is a receptor involved in the regulation of satiety</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>(5HT2C)</td>
<td>• The T allele confers a protective effect against risk of weight gain with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T/T)</td>
<td>atypical antipsychotics as compared to the C allele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Lowest weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>risk]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine 2 Receptor</td>
<td>DRD2 is a receptor affected by dopamine in the brain</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>(DRD2)</td>
<td>• DRD2 is involved in response to antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C/C)</td>
<td>• This genotype confers normal activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catechol-O-Methyl</td>
<td>COMT is an enzyme responsible for breakdown of dopamine in the frontal lobes of the</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>Methyltransferase (COMT)</td>
<td>brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Val/Met)</td>
<td>• COMT is involved in response to stimulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Normal]</td>
<td>• This genotype confers normal activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-2A Adrenergic</td>
<td>ADRA2A is a receptor which plays an important role in neurotransmitter release</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>Receptor (ADRA2A)</td>
<td>• ADRA2A is involved in response to stimulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C/C)</td>
<td>• This genotype confers normal activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Normal response]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µ-Opioid Receptor</td>
<td>OPRM1 is an opioid receptor which is affected by natural and synthetic compounds</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>(OPRM1)</td>
<td>• OPRM1 is involved in response to opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A/A)</td>
<td>• This genotype confers normal activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Normal response]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate Receptor</td>
<td>GRIK1 is an excitatory neurotransmitter receptor</td>
<td></td>
<td>There are no known gene-drug interactions for this genotype</td>
</tr>
<tr>
<td>Kainate 1 (GRIK1)</td>
<td>• GRIK1 is involved in response to topiramate for alcohol abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A/A)</td>
<td>• This genotype confers normal activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Normal response]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Results Report: Pharmacokinetic Gene Variations; CYP450 Drug Metabolism

<table>
<thead>
<tr>
<th>Gene Result</th>
<th>Therapeutic Implications</th>
<th>Interaction</th>
<th>Clinical Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6 IM</td>
<td><strong>Intermediate metabolizer:</strong> ↑ risk of elevated serum levels and drug interactions</td>
<td><img src="image" alt="Warning" /></td>
<td>Use caution with medications metabolized by CYP2B6. See Drug Interaction Summary for details.</td>
</tr>
<tr>
<td>*6/*6</td>
<td>• A dose adjustment or alternate therapy may be necessary</td>
<td><img src="image" alt="Caution" /></td>
<td></td>
</tr>
<tr>
<td>Intermediate activity</td>
<td></td>
<td><img src="image" alt="Caution" /></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 PM</td>
<td><strong>Poor metabolizer:</strong> ↑ risk of elevated serum levels and drug interactions</td>
<td><img src="image" alt="Warning" /></td>
<td>Use caution with medications metabolized by CYP2C19. See Drug Interaction Summary for details.</td>
</tr>
<tr>
<td>*2/*6</td>
<td>• A dose adjustment or alternate therapy may be necessary</td>
<td><img src="image" alt="Caution" /></td>
<td></td>
</tr>
<tr>
<td>Low activity</td>
<td></td>
<td><img src="image" alt="Caution" /></td>
<td></td>
</tr>
<tr>
<td>CYP1A2 EM</td>
<td>Variations in the CYP1A2 liver enzyme can result in altered drug metabolism and unexpected drug serum levels</td>
<td><img src="image" alt="Ok" /></td>
<td>There are no known gene-drug interactions for this genotype.</td>
</tr>
<tr>
<td>*1A/*1A</td>
<td>• This genotype confers normal activity</td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>Normal activity</td>
<td></td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>CYP2C9 EM</td>
<td>Variations in the CYP2C9 liver enzyme can result in altered drug metabolism and unexpected drug serum levels</td>
<td><img src="image" alt="Ok" /></td>
<td>There are no known gene-drug interactions for this genotype.</td>
</tr>
<tr>
<td>*1/*2</td>
<td>• This genotype confers normal activity</td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>Normal activity</td>
<td></td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 EM</td>
<td>Variations in the CYP2D6 liver enzyme can result in altered drug metabolism and unexpected drug serum levels</td>
<td><img src="image" alt="Ok" /></td>
<td>There are no known gene-drug interactions for this genotype.</td>
</tr>
<tr>
<td>*2/*2</td>
<td>• This genotype confers normal activity</td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>Normal activity</td>
<td></td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>CYP3A4/CYP3A5</td>
<td>Variations in the CYP3A4/5 liver enzymes can result in altered drug metabolism and unexpected drug serum levels</td>
<td><img src="image" alt="Ok" /></td>
<td>There are no known gene-drug interactions for this genotype.</td>
</tr>
<tr>
<td>*1/*1</td>
<td>• This genotype confers normal activity</td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>*3/*3</td>
<td>• CYP3A activity is determined by the sum activity of the CYP3A family of genes; in adults the most influential are CYP3A4 and 3A5</td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
<tr>
<td>Normal activity</td>
<td></td>
<td><img src="image" alt="Ok" /></td>
<td></td>
</tr>
</tbody>
</table>

Interpretation

- Lack of efficacy for SSRI’s could be related to the SLC6A4 or 2C19 variants

- SNRIs and atypical antidepressants are relevant for this patient; clinician decided to prescribe duloxetine

- Caution with any drugs metabolized by 2C19 or 2B6

---

**Drug Interaction Summary:**

This summary provides a listing of implications for psychotropic and pain medications specific to your patient’s genetic profile.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Primary metabolizing enzyme(s)</th>
<th>No known gene-drug interactions</th>
<th>Options which may be used if clinically indicated</th>
<th>Serum levels may be ↓ [reduced dose may be required]</th>
<th>Serum levels may be ↓ [increased dose may be required]</th>
<th>Increased risk for adverse events or poor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa®)</td>
<td>2C19, 3A4/5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram (Lexapro®)</td>
<td>2C19, 2D6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>2D6, 2C9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (Luvox®)</td>
<td>2D6, 1A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil®)</td>
<td>2D6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SSRIs**

- Desvenlafaxine (Pristiq®)
- Duloxetine (Cymbalta®)
- Levomilnacipran (Fetzima®)
- Venlafaxine (Effexor®) [1]
- Bupropion (Wellbutrin®)
- Mirtazapine (Remeron®)
- Trazodone (Desyrel®, Oleptro®)
- Viltroxone (Vibryd®)
- Vortioxetine (Brintellix®)

**SNRIs**

- Indeterminate [2]

---

[1] Prodrug - requiring activation by the liver; 2D6 IMS/PMs may experience lower efficacy and increased side effects due to reduced conversion to the active metabolite and higher levels of the inactive parent drug; 2D6 UM may experience increased conversion of the parent drug, and higher levels of the active metabolite.

[2] Indeterminate - Gene-drug interaction may exist, however indeterminate due to varied impact of multiple CYP450 enzymes, unknown clinical significance of a rare variation, or genotype was unable to be determined.

---

CACNA1C variation in combination with clinical presentation, led clinician to try lurasidone.

Careful monitoring of weight gain was warranted due to the MC4R variation. An exercise regime was recommended due the presence of this variant as well as the BDNF variation.
L-methylfolate and Omega-3 fatty acids were also added to the patients regimen due to the presence of variations in MTHFR and CACNA1C.
Follow-up

- Patient reported
  - Stable mood, with no new depressive episodes
  - No sexual side effects
  - Reduction of HAM-D from 20 to 5
  - Reduction of depressive thoughts, suicidal ideation, and mood swings has allowed him to become more productive in work and in his social life
  - Compliant with regimen and exercise plan

<table>
<thead>
<tr>
<th>Prior Treatment</th>
<th>GeneceptAssay Guided Treatment</th>
<th>Relevant Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Duloxetine</td>
<td>2D6, SLC6A4, BDNF</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lurasidone</td>
<td>3A4, CACNA1C, MC4R</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td>BDNF</td>
</tr>
<tr>
<td>L-methylfolate</td>
<td></td>
<td>MTHFR</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td></td>
<td>CACNA1C</td>
</tr>
</tbody>
</table>
Contact Information

Genomind, Inc.
2200 Renaissance Blvd, Suite 100
King of Prussia, PA 19406-2755
877.895.8658

customerservice@genomind.com
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