



White Paper

The Science Behind the Genecept Assay™

January, 2016

INTRODUCTION

Genomind, a personalized medicine company bringing innovation to mental healthcare through genetic testing, is pleased to present this summary of the science behind the Genecept Assay™, a genetic test which analyzes both pharmacokinetic and pharmacodynamic genes. As of January 2016, an expanded panel from the original Genecept Assay will be launched, with 8 additional genes (5 pharmacodynamic genes and 3 pharmacokinetic genes). The additional genes are displayed in orange font below. The assay is used to assist clinician decision-making when prescribing medication for psychiatric conditions. It is a simple non-invasive buccal (cheek swab) test that can be administered quickly in the clinician's office. The comprehensive results report provides clear clinical implications, and a complimentary consultation with experts in the field of psychopharmacogenetics is available with each report.

Background on the Assay

The Genecept Assay is a genetic test developed by Genomind to assess variations in deoxyribonucleic acid (DNA) which may alter gene function and response to psychotropic therapies. Psychiatric practice is uniquely challenging because of the variability in treatment response, even with the application of treatment guidelines; this leads many clinicians to utilize a trial and error approach during treatment planning. Moreover, it is difficult to determine in advance if a patient will respond to a medication, or whether they will experience adverse events which may force discontinuation. Differences in patient response patterns may be partially explained by underlying genetic and biochemical disparities. The Genecept Assay sheds light on these differences to help the clinician arrive at informed and personalized therapeutic decisions.

The Assay analyzes 18 genes which have been shown in numerous clinical studies to have implications for response to treatments used in depression, anxiety, OCD, ADHD, bipolar disorder, PTSD, autism, schizophrenia, chronic pain and substance abuse. The genes assessed by the Assay target major hepatic enzymes and key neurotransmitter pathways including serotonin, dopamine, norepinephrine and glutamate. These genes can be further categorized as:

- **Pharmacodynamic:** those which relate to the effect of the drug on the body, including interactions with receptors, transporters and neurotransmitters.
- **Pharmacokinetic:** those which relate to the effect of the body on the drug, including drug metabolism.

Genes in the Panel

Pharmacodynamic Genes:

Serotonin Transporter (SLC6A4) ¹⁻¹²

SLC6A4 is a presynaptic transmembrane protein, responsible for serotonin reuptake¹. Antidepressant activity of SSRI medications is achieved through inhibition of this protein¹. Two variations in *SLC6A4* are tested, within the serotonin-transporter-linked polymorphic region (5-HTTLPR).

- 5-HTTLPR is a 43 or 44 basepair deletion of DNA in *SLC6A4*. Patients who have a deletion of this section are termed "short" or **S** patients. Patients who do not have this deletion are termed "long" or **L** patients. Studies have repeatedly shown that the "short" variant is associated with a reduction in both the expression and function of the serotonin transporter²⁻⁷.

- In addition to the long/short variation, the Genecept Assay also tests for a single nucleotide polymorphism (SNP), within the long (L) 44 basepair section, which causes impaired function similar to the “short” variant. This variation is represented by either an L(A) or an L(G), and patients who possess the L(G) allele have poor expression/function of the serotonin transporter²⁻⁷.

Individuals with these variations may have reduced reuptake of synaptic serotonin¹, and several studies have shown an association to lower stress resilience and higher rates of PTSD^{11,12}. Retrospective studies have also shown that individuals with these variations [S or L(G)] may be more likely to have a poor response, slow response, or increased risk for adverse events during treatment with SSRI medications, as compared to individuals who do not possess these variants²⁻⁹. One should use caution with SSRI medications which include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Alternative interventions, such as SNRIs or atypical antidepressants that do not primarily target the serotonin transporter protein may be relevant in these patients.

Calcium Channel, L-type Voltage-gated, Alpha-1C Subunit (CACNA1C) ¹³⁻³⁷

CACNA1C is important in the regulation of calcium signaling^{13,14}. Several genome wide association studies (GWAS) have identified a variant in this gene, the A allele, to be associated with conditions related to mood instability and lability¹⁶⁻²³. Variations in this gene may lead to ion channel dysfunction, resulting in a prolongation of the period during which the pore remains open, leading to increased excitatory signaling^{13,17}. It has also been reported that this variant is associated with changes in amygdala volume³⁰, frontal-hippocampal function^{22,29}, disruptions in cognition in both schizophrenic³² and bipolar patients³³, and has been hypothesized to be related to glutamate signaling²⁸. The implications of this variant for treatment are not fully understood, however if clinically relevant, traditional mood stabilizers, atypical antipsychotic medications, or omega-3 fatty acids (ω-3 FA) may be relevant to reduce the excess excitatory calcium signaling resulting from this variation. Various meta-analyses have validated the utility of ω-3 FA for bipolar depression (but not mania)³⁴⁻³⁷. These studies suggest that antidepressant effects of ω-3 FA may be largely dependent on the fatty acid eicosapentaenoic acid (EPA). While the antidepressant efficacy of ω-3 FA is not fully understood, it may be related to stabilization of calcium and/or sodium channels.

Sodium Channel Component, Ankyrin-G (ANK3) ^{14,16,18,23,25,34-46}

ANK3 belongs to a family of scaffolding proteins known as the ankyrins, and plays a role in the maintenance of sodium ion channels³⁸. A variation in this gene, the T allele, can potentially lead to abnormal clustering of sodium channels and dysfunction in action potential firing³⁸. GWAS have shown a correlation between this variation and disorders characterized by mood instability and lability^{16,18,23,39-42}. Many studies indicate that this variant is associated with changes in anatomical connections which may be related to cognitive and affective symptoms^{25,42-45}. More specifically, this variation has been associated with anhedonia, altered novelty seeking, impaired threat/stress signal processing, poorer cognition, and reduced integrity of white matter tracts⁴¹. As with the variant in CACNA1C, the therapeutic implications of this variation are not yet fully understood. Where clinically appropriate, traditional mood stabilizers or ω-3 FA may be relevant to reduce excess excitatory signaling by sodium channels. Various meta-analyses have validated the utility of ω-3 FA for bipolar depression (but not mania)³⁴⁻³⁷. These studies suggest that antidepressant effects of ω-3 FA may be largely dependent on the fatty acid eicosapentaenoic acid (EPA). While the antidepressant efficacy of ω-3 FA is not fully understood, it may be related to stabilization of calcium and/or sodium channels.

Serotonin Receptor 2C (5HT2C) ^{7,47-59}

5HT2C is one site by which various neuroleptic medications act. Serotonin acting at this receptor is involved in the regulation of appetite, and is one mechanism utilized to signal satiety^{47,50}. Inhibition of this signaling pathway via 5HT2C antagonism (or blocking) has been shown in clinical studies to lead to increased food intake^{48,50,55}. In patients taking atypical antipsychotics, a variation in *5HT2C*, the **C** allele, confers risk for weight gain, while the **T** allele demonstrates a protective effect^{49,55}. Greater clinical vigilance related to weight gain and metabolic syndrome may be indicated for individuals when taking atypical antipsychotics, including assessment of blood sugar and lipids. Several double-blind placebo-controlled studies have shown significant weight loss in post-menopausal women and women with polycystic ovarian syndrome treated with inositol, an insulin sensitizing agent⁵⁷⁻⁵⁹. As many atypical antipsychotics have been shown to decrease insulin sensitivity⁵⁵, supplementation with inositol may help to ameliorate the metabolic side effects associated with atypicals.

Melanocortin 4 Receptor (MC4R) ^{56,60-65}

MC4R is expressed in various sites of the brain, including the hypothalamus and has a central role in the regulation of satiety, body weight, and energy balance⁶⁰. Over 70 variations in *MC4R* have been identified, and about half of these variants result in partial or total loss of function, which may lead to hyperphagia, hyperinsulinemia, binge eating, food-seeking behavior, and excessive hunger⁶¹. Moreover, studies have shown that a particular variation in this gene, the **A** allele, is associated with increased risk of weight gain which is exacerbated by atypical antipsychotics^{62,63}. When weight is a concern, clinicians should use caution when prescribing atypical antipsychotics. In general, those which pose a high risk for weight gain are clozapine and olanzapine, while aripiprazole, loperidone, paliperidone, quetiapine, and risperidone are medium risk medications, and asenapine, brexpiprazole, cariprazine, lurasidone, and ziprasidone tend to be lower risk medications^{56,64,65}.

Dopamine 2 Receptor (DRD2) ⁶⁶⁻⁶⁹

DRD2 is involved in movement and perception. Most neuroleptics act through blockade of the D₂ receptor to inhibit dopamine signaling; affinity for this receptor has been shown to correspond to risk for and degree of side effects with these medications⁶⁶. The deletion (**DEL**) variant reduces gene expression in vitro, resulting in reduced D₂ receptor density^{66,69}, and increased risk for poor response and adverse events with antipsychotic medications^{67,68}. Caution with antipsychotics is warranted, and agents with lower binding affinity to the D₂ receptor may be relevant.

Catechol-O-Methyltransferase (COMT) ⁷⁰⁻⁸⁵

COMT is an enzyme responsible for breakdown of dopamine in the frontal lobes of the brain⁷⁵. Dopamine levels here are critical for memory, attention, judgment and other executive functions⁷⁴. A valine (Val) to methionine (Met) variation results in varied capacity of the enzyme to degrade dopamine⁷⁵. The Met allele results in reduced enzymatic activity, while the Val allele results in increased activity⁷⁵. Patients who have normal levels of dopamine degradation possess one increased and one decreased function allele (**Val/Met**). Patients with the **Val/Val** genotype display elevated enzyme activity and increased dopamine degradation; conversely, patients who are **Met/Met** have reduced enzyme activity and dopamine degradation⁷⁵. Clinical studies have shown that the Val/Val genotype may have behavioral consequences regarding cognitive function, memory, attention, motivation and judgment⁷⁰⁻⁷³. In Val/Val (high activity) patients, dopaminergic agents have been shown to improve executive function and working memory in both animal and human studies⁷⁵⁻⁷⁸; however, these agents may produce a deleterious effect on cognition in Met/Met (low activity) patients⁷⁸.

Alternative therapeutic strategies include transcranial magnetic stimulation (TMS) for Val/Val patients. As stated previously, the increased activity of the Val/Val genotype can result in a hypo-dopaminergic state. Studies in rats have shown that TMS can increase dopamine outflow compared to sham stimulation. Additionally, studies in humans have demonstrated TMS can be beneficial for patients suffering from depression, potentially by increasing dopamine levels in the prefrontal cortex. Based on these studies it is thought that TMS may be an effective strategy in patients who are *COMT* Val/Val via stimulation of dopamine release.⁷⁹⁻⁸⁵

Alpha-2A Adrenergic Receptor (ADRA2A)⁸⁶⁻⁹³

ADRA2A encodes a subtype of alpha 2 adrenergic receptors. Norepinephrine (NE) is the main catecholamine which signals via adrenergic receptors, and ADRA2A is the major receptor subtype found in the brain, particularly the prefrontal cortex (PFC)⁸⁶. NE and the PFC are both critical for working memory and executive function, such as regulating attention, impulse control, and inhibiting inappropriate behavior⁸⁷. NE stimulates ADRA2A to improve PFC function, including attention regulation and working memory⁸⁶⁻⁸⁸. Studies have shown that ADRA2A dysregulation is associated with impaired PFC function and ADHD⁸⁶⁻⁸⁸.

Children and adolescents being treated for ADHD symptoms are likely to have an **increased response** to stimulants if they are carriers of a **G** allele variant in *ADRA2A*⁹¹⁻⁹³. For example, two studies have shown that methylphenidate (MPH) improved inattentive symptoms in G allele carriers based on the Swanson, Nolan, and Pelham Scale version IV (SNAP-IV) rating scale^{92,93}. MPH increases synaptic levels of dopamine and NE⁸⁹; increased NE may bind and stimulate ADRA2A to improve PFC function. The exact mechanism of this drug-gene effect of MPH and ADRA2A has not been fully elucidated. However, an animal study demonstrated that MPH activity was inhibited when co-administered with an ADRA2A blocker, suggesting ADRA2A is involved in the mechanism of action of MPH⁹⁰.

Methylenetetrahydrofolate reductase (MTHFR)⁹⁴⁻¹⁰²

MTHFR is an enzyme responsible for catalyzing the conversion of folic acid to methylfolate. Methylfolate is the active form of folic acid, a vital precursor for the synthesis of norepinephrine, dopamine and serotonin⁹⁴. Two variations are tested for within this gene. The **T** allele of C677T, and **C** allele of A1298C lead to reduced enzymatic activity of MTHFR, resulting in inefficient folic acid metabolism and production of methylfolate^{95,96}. Several studies have shown these variations are associated with depression, bipolar disorder, and schizophrenia⁹⁷. Studies in psychiatric patients analyzing the therapeutic efficacy of L-methylfolate found superior outcomes when SSRI/SNRI treatment was supplemented with L-methylfolate, compared to SSRIs/SNRIs alone⁹⁹⁻¹⁰². Preliminary data also suggests that biomarkers related to L-methylfolate synthesis and/or metabolism may identify patients who would benefit from supplementation with L-methylfolate¹⁰².

Brain-derived Neurotrophic Factor (BDNF)¹⁰³⁻¹²¹

BDNF plays a role in regulating the growth, development, and survival of neurons as well as the release of neurotransmitters¹⁰³. BDNF serves as a candidate gene for depression as a variation in this gene, the **Met** allele, is associated with reduced BDNF secretion, depression and altered stress reactivity^{103,106-108,110,113}. Studies have suggested that Caucasian Met carriers have poorer response to SSRIs (escitalopram, citalopram, paroxetine, fluoxetine, sertraline, and fluvoxamine) compared to Val/Val patients, but this data is preliminary and awaits replication^{116,118}. Additionally, this association was not found in Asian patients^{103,114,116}. Several studies indicate that physical activity may improve cognition and working memory in Met carriers and may be used if clinically indicated¹¹⁹⁻¹²¹.

μ-Opioid Receptor (OPRM1) ¹²²⁻¹²⁵

Mu-opioid receptors are located throughout brain circuits that are involved in processing rewards, analgesia, and stress response¹²². OPRM1 is the main target for many natural and synthetic compounds including opioid medications¹²². A variation in this gene, the **G** allele, has been linked to reduced expression levels of OPRM1¹²². Clinically, this variation has been linked to higher pain intensity, more pain, as well as slower recovery from certain injuries like a herniated disk¹²². Studies have also found that patients with the G allele may need higher doses of opioids to achieve analgesia, however these patients may be at risk for opioid dependence¹²²⁻¹²⁵. The research related to the risk for opioid dependence is varied and may be an ethnicity-dependent effect¹²²; further research is needed to elucidate the impact of the G allele on opioid dependence in all populations. Caution and careful monitoring may be required however opioids are not contraindicated in these individuals. Non-opioid analgesics may be a therapeutic option for these patients if clinically indicated.

Glutamate Receptor Kainate 1 (GRIK1) ¹²⁶⁻¹²⁸

Topiramate is a promising anticonvulsant medication used to treat alcohol dependence. However, response to topiramate varies. Topiramate blocks highly selective glutamate receptors, most notably receptors with the GRIK1 subunit. GRIK1 helps to assemble these excitatory glutamate receptors which are involved in various neurological processes. Polymorphisms in this gene have been shown to predict response to topiramate¹²⁶⁻¹²⁸. A polymorphism in *GRIK1*, the **C** allele, has been associated with **improved topiramate response** for alcohol abuse¹²⁶⁻¹²⁸. However, the exact mechanism by which the C allele moderates this effect remains undetermined¹²⁸. Topiramate may be used for alcohol dependence/abuse in patients with the C allele where clinically indicated.

Pharmacokinetic Genes:

Cytochrome P450 (CYP450) ^{7, 54,129-200}

CYP450s are a family of hepatic enzymes which catalyze the breakdown of various substances^{54,131-134}. **CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6,** and **CYP3A4/5** are responsible for the degradation of a large number of psychotropic medications, and variations in the genes encoding for these enzymes can alter their activity resulting in unexpected drug serum levels, altered efficacy and adverse events^{7,54,129-200}. For **CYP1A2, CYP2B6, CYP2C9, CYP2C19,** and **CYP2D6**, patients with normal rates of drug metabolism are extensive metabolizers (**EM**). Patients exhibiting the intermediate (**IM**) or poor metabolizer (**PM**) phenotype (intermediate or low activity) may have reduced enzyme activity resulting in increased risk for elevated drug serum levels, drug-drug interactions and/or reduced production of active metabolites. Reduced doses of medications metabolized by these systems may be clinically appropriate^{137,149,159,160,164,169,170,184}. The ultra-rapid metabolizer (**UM**) phenotype (high/fast activity) may lead to elevated enzyme activity resulting in increased risk for sub-therapeutic drug serum levels, poor efficacy and adverse events associated with metabolite build up; increased doses of medications metabolized by these systems may be clinically appropriate^{137,149,159,160,164,169,170-176}.

CYP1A2 activity can result in the same metabolizer phenotypes as the previously mentioned CYPs; PM or IM indicating reduced metabolism, or EM indicating normal metabolism^{54,129-143}. Additionally, CYP1A2 may also be greatly affected by the presence of inducers, leading to increased metabolism. A particular variation in this gene, *1F, affects how potently inducers may increase CYP1A2 activity¹⁴¹⁻¹⁴⁸. The presence of this variant may increase the metabolism of a drug **in the presence of inducers** such as certain cruciferous vegetables or tobacco smoke, as well as other medications¹⁴¹⁻¹⁴⁸ (see the Genecept Assay Report Interpretation Guide for which substances are most likely to lead to induction of CYP1A2).

Lastly the combinatorial effects of CYP3A enzymes, including CYP3A4 and CYP3A5, are responsible for the overall metabolism of CYP3A substrates. Variations in CYP3A4 and CYP3A5 can affect the rate of metabolism for CYP3A substrates and the combined phenotype is reported as **slow**, **normal**, or **fast** activity. Patients who have fast CYP3A4/5 activity may display elevated levels of metabolism, which may lead to an increased risk for sub-therapeutic drug serum levels, poor efficacy and adverse events associated with metabolite build up; increased doses of medications metabolized by this system may be clinically appropriate^{54,131-134,137,150}. Patients who are slow metabolizers for CYP3A4/5 may have reduced enzyme activity resulting in increased risk for elevated drug serum levels, drug-drug interactions and/or reduced production of active metabolites^{54,131-134,137,150}.

	Gene	Physiological Role	Impact of Mutation	Treatment Impact
Pharmacodynamic	Serotonin Transporter (SLC6A4)	Protein responsible for reuptake of serotonin from the synapse	Inhibition of this protein by SSRIs, which may lead to increased risk for non-response/side effects	Use caution with SSRIs; atypical antidepressants or SNRIs may be used if clinically indicated
	Calcium Channel (CACNA1C)	A subunit of the calcium channel which mediates excitatory signaling	Associated with conditions characterized by mood instability/lability	Atypical antipsychotics, mood stabilizers, and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated
	Sodium Channel (ANK3)	Protein that plays a role in sodium channel function and regulation of excitatory signaling	Associated with conditions characterized by mood instability/lability	Mood stabilizers and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated
	Serotonin Receptor 2C (5HT2C)	Receptor involved in regulation of satiety	Blocked by atypical antipsychotics, resulting in metabolic side effects	Use caution with atypical antipsychotics; inositol may be used to mitigate risk for weight gain if clinically indicated
	Melanocortin 4 Receptor (MC4R)	Receptor that plays a role in the control of food intake	Increased risk for weight gain and higher BMI, which is exacerbated by atypical antipsychotics	Use caution with atypical antipsychotics
	Dopamine 2 Receptor (DRD2)	Receptor affected by dopamine in the brain	Blocked by antipsychotic medications and is associated with risk for non-response/side effects	Use caution with antipsychotics
	Catechol-O-Methyltransferase (COMT)	Enzyme primarily responsible for the degradation of dopamine in the frontal lobes of the brain	Altered dopamine states can have emotional/behavioral effects and impact response to dopaminergic agents	Dopaminergic agents or TMS may be used if clinically indicated for Val/Val patients Use caution with dopaminergic agents in Met/Met patients
	Alpha-2A Adrenergic Receptor (ADRA2A)	Receptor involved in neurotransmitter release	Associated with improved response to stimulant agents	Stimulant agents may be used if clinically indicated
	Methylenetetrahydrofolate Reductase (MTHFR)	Predominant enzyme that converts folic acid/folate to its active form (methylfolate) needed for synthesis of serotonin, dopamine, and norepinephrine	Associated with varied activity and conversion of folic acid/folate to methylfolate	Supplementation with L-methylfolate may be used if clinically indicated
	<ul style="list-style-type: none"> • A1298C • C677T 			
	Brain-derived Neurotrophic Factor (BDNF)	Important for proper neuronal development and neural plasticity	Impaired BDNF secretion, which may be associated with altered SSRI response in Caucasians	Increased physical activity/exercise may be beneficial for Met carriers if clinically indicated
μ-Opioid Receptor (OPRM1)	Opioid receptor affected by natural and synthetic compounds	Activated by opioids and associated with varied analgesic response, dosage, and abuse/addiction risk	Use caution with opioids; non-opioid analgesics may be used if clinically indicated	
Glutamate Receptor (GRIK1)	An excitatory neurotransmitter receptor in the brain	Associated with response to topiramate for alcohol abuse	Topiramate may be used for treatment of alcohol abuse if clinically indicated	
Pharmacokinetic (CYP450s)	CYP1A2	Enzymes that metabolize medications in the liver	Large number of psychiatric medications are metabolized by CYP450s	Dose adjustment (an increase or decrease) may be required
	CYP2B6			
	CYP2C9			
	CYP2C19			
	CYP2D6			
	CYP3A4/5			

= newly added to the Genecept Assay, January 2016.

Using Genetic Information to Inform Treatment Planning

Genetic results provide one piece of evidence for the heterogeneity observed in medication response. They offer information about the likelihood that a patient will respond to a medication therapy and/or experience adverse events or drug interactions. Pharmacodynamic results describe the underlying biochemistry of presenting symptoms and adverse events, while pharmacokinetic results guide dosing decisions to optimize response. Treatment decisions informed by these genetic results offer a personalized treatment plan to objectively address presenting symptoms and side effects. The genes analyzed in the Genecept Assay are associated with a wide range of psychotropic medications and can help to inform treatment plans for depression, anxiety, OCD, ADHD, bipolar disorder, PTSD, autism, schizophrenia, chronic pain and substance abuse.

References

References can be found in the Literature Summary, which is available at your request by calling 877-895-8658 or emailing customerservice@genomind.com.