Dynacare®

GENOMIND®

White Paper

The Genes Analyzed by the Genecept Assay®

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INTRODUCTION

Dynacare is pleased to present this summary of the genes behind the Genecept Assay®, a genetic test that analyzes both pharmacokinetic and pharmacodynamic genes. The current test includes the analysis of 12 pharmacodynamic genes and six pharmacokinetic CYP450 genes. 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 patient report.

Background on the Assay

The Genecept Assay is a genetic test developed by Genomind to assess variations in deoxyribonucleic acid (DNA) that 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 whether a patient will respond to a medication or experience adverse events that 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 that have been shown in numerous clinical studies to have implications for response to treatments used for 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 follows:

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

Genes Analyzed by the Test

Pharmacodynamic Genes

Serotonin Transporter (SLC6A4) [1-24]

SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake.[1] Antidepressant activity of SSRI medications is achieved through inhibition of this protein.[1] Two variations in *SLC6A4* are tested, within the serotonin-transporter-linked polymorphic region (5-HTTLPR).

- 5-HTTLPR is a 43- or 44-base-pair 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 transporter.[2-7]
- In addition to the long/short variation, the Genecept Assay also tests for a single nucleotide polymorphism (SNP) within the long (L) 44-base-pair 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 transporter.[2-7]

Individuals with these variations may have reduced reuptake of synaptic serotonin,[1] and several studies have shown an association with lower stress resilience and higher rates of PTSD.[11,12] Individuals who are homozygous for either of the two risk alleles [**S or L(G)**] have also been shown to have an increased risk for abnormal cortisol release in response to stressors.[17-21] 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 variants.[2-9] More specifically, individuals who carry only a single risk variant [**S or L(G)** alone] appear to be more at risk for adverse reactions, whereas the **S/S, S/L(G)** and **L(G)/L(G)** homozygotes are at a greater risk of non-response and adverse effects. One should use caution with SSRI medications that include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Alternative interventions, such as SNRIs or non-SSRI 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) [25-55]

CACNA1C is important in the regulation of calcium signaling.[25,26] 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 lability.[27-35] 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.[25,29] It has also been reported that this variant is associated with changes in amygdala volume,[42] frontal-hippocampal function,[33,41] and disruptions in cognition in both schizophrenic[44] and bipolar patients,[45] and this variant also has been hypothesized to be related to glutamate signaling.[40] 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 (ώ-3 FA) may be used to reduce the excess excitatory calcium signaling resulting from this variation. Various meta-analyses have validated the utility of ώ-3 FA for bipolar depression (but not mania).[46-49] These studies suggest that antidepressant effects of ώ-3 FA may be largely dependent on the fatty acid eicosapentaenoic acid (EPA).

Sodium Channel Component, Ankyrin-G (ANK3) [26-28,30,35,37,46-49,56-64]

ANK3 belongs to a family of scaffolding proteins known as the ankyrins, and plays a role in the maintenance of sodium ion channels.[56] A variation in this gene, the **T** allele, can potentially lead to abnormal clustering of sodium channels and dysfunction in action potential firing.[56] GWAS have shown a correlation between this variation and disorders characterized by mood instability and lability.[27-28,30,35,57-60] Many studies indicate that this variant is associated with changes in anatomical connections that may be related to cognitive and affective symptoms.[37,60-63] 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 tracts.[59] As with the variant in *CACNA1C*, the therapeutic implications of this variation are not yet fully understood. Where clinically appropriate, traditional mood stabilizers or ώ-3 FA may be used to reduce excess excitatory signaling by sodium channels. Various meta-analyses have validated the utility of ώ-3 FA for bipolar depression (but not mania).[46-49] These studies suggest that antidepressant effects of ώ-3 FA may be largely dependent on the fatty acid eicosapentaenoic acid (EPA). While the antidepressant efficacy of ώ-3 FA is not fully understood, it may be related to stabilization of calcium and/or sodium channels.

Serotonin Receptor 2C (5HT2C) [7, 65-75]

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.[65,68] Inhibition of this signaling pathway via 5HT2C antagonism (or blocking) has been shown in clinical studies to lead to increased food intake.[66,69,73] 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.[67,69,73] 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. Medications that have been shown to decrease atypical antipsychotic-induced weight gain include metformin, which is traditionally used in type II diabetes and other metabolic disorders, and lorcaserin, an anti-obesity drug that signals through the 5HT2C receptor.[271]

Melanocortin 4 Receptor (MC4R) [74, 76-82]

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 balance.[76] 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 hunger.[77] 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.[78-79] When weight is a concern, clinicians should use caution when prescribing atypical antipsychotics. In general, those that pose a high risk for weight gain are clozapine and olanzapine, while aripiprazole, iloperidone, paliperidone, quetiapine and risperidone are medium-risk medications, and asenapine, brexpiprazole, cariprazine, lurasidone and ziprasidone tend to be lower-risk medications.[74,80-81]

Dopamine 2 Receptor (DRD2) [83-87]

DRD2 is involved in movement and perception. Most neuroleptics act through antagonism of the D_2 receptor to inhibit dopamine signaling. The deletion (**DEL**) variant reduces gene expression in vitro, resulting in reduced D_2 receptor density[83,86] and increased risk for poor response and adverse events (predominately weight gain) with antipsychotic medications,[84-85] Caution with antipsychotics is warranted. The deletion (**DEL**) allele is also associated with increased risk for opioid dependence, with homozygotes at even greater risk.[87]

Catechol-O-Methyltransferase (COMT) [88-117]

COMT is an enzyme responsible for breakdown of dopamine in the frontal lobes of the brain.[88] Dopamine levels here are critical for memory, attention, judgment and other executive functions.[92] A valine (**Val**) to methionine (**Met**) variation results in varied capacity of the enzyme to degrade dopamine.[88,103] The **Met** allele results in reduced enzymatic activity, while the **Val** allele results in increased activity.[88,103] 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 degradation.[88,103] Clinical studies have shown that the **Val/Val** genotype may have behavioral consequences regarding cognitive function, memory, attention, motivation and judgment.[88-91] In **Val/Val** (high-activity) patients, dopaminergic agents have been shown to improve executive function and working memory in both animal and human studies;[93-94,103-104] however, these agents may produce a deleterious effect on cognition in **Met/Met** (low-activity) patients.[104] Another class of drugs known as COMT inhibitors have also been shown to produce this biphasic effect on

cognition in **Val/Val** and **Met/Met** individuals, and may be clinically useful in patients with impaired executive function.[103-110] Recent clinical studies investigating the effects of antipsychotic medications on cognitive function in schizophrenia and bipolar disorder found that patients with the **Met/Met** genotype had improved scores on measures of executive function (as well as positive symptoms of schizophrenia) when compared with their **Val/Met** and **Val/Val** counterparts.[111-117]

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 with 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.[95-101]

Alpha-2A Adrenergic Receptor (ADRA2A) [118-125]

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).[118] NE and the PFC are both critical for working memory and executive function measures, such as regulating attention, controlling impulses and inhibiting inappropriate behavior.[119] NE stimulates ADRA2A to improve PFC function, including attention regulation and working memory.[118-120] Studies have shown that ADRA2A dysregulation is associated with impaired PFC function and ADHD.[118-120]

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.*[123-125] 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.[124-125] MPH increases synaptic levels of dopamine and NE;[121] 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 MPH.[122]

Methylenetetrahydrofolate reductase (MTHFR) [126-138]

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 serotonin.[126] Two variations are tested within this gene. The **T** allele of C677T and the **C** allele of A1298C lead to reduced enzymatic activity of MTHFR, resulting in inefficient folic acid metabolism and production of methylfolate.[127-128] Several studies have shown these variations are associated with depression, bipolar disorder and schizophrenia.[129] Studies in psychiatric patients analyzing the therapeutic efficacy of L-methylfolate found superior outcomes when SSRI/SNRI treatment was supplemented with L-methylfolate compared with SSRIs/SNRIs alone.[131-134] A 2016 study with a methylfolate B-vitamin complex showed depression remission rates of 42% as monotherapy when MTHFR genotype was taken into consideration.[136] Preliminary data also suggests that biomarkers related to L-methylfolate synthesis and/or metabolism may identify patients who would benefit from supplementation with L-methylfolate.[102]

Brain-derived Neurotrophic Factor (BDNF) [139-161]

BDNF plays a role in regulating the growth, development and survival of neurons as well as the release of neurotransmitters.[139] BDNF may serve as a candidate gene for depression. A variation in this gene, the **Met** allele, is associated with reduced BDNF secretion, depression and altered stress reactivity.[139,142,144,146,149] Studies have suggested that Caucasian **Met** carriers have poorer response to SSRIs (escitalopram, citalopram, paroxetine, fluoxetine, sertraline and fluvoxamine) compared with **Val/Val** patients, but this data is preliminary and awaits replication.[152,154] Additionally, this association was not found in Asian patients.[139,150,152] Several studies indicate that physical activity may improve cognition and working memory in **Met** carriers and may be implemented as therapy,if clinically indicated.[155-157]

μ-Opioid Receptor (OPRM1) [162-172]

Mu-opioid receptors are located throughout brain circuits that are involved in processing rewards, analgesia and stress response.[162] OPRM1 is the main target for many natural and synthetic compounds including opioid medications.[162] A variation in this gene, the **G** allele, has been linked to reduced expression levels of OPRM1.[162] Clinically, this variation has been linked to higher pain intensity, more pain, and slower recovery from certain injuries such as a herniated disc.[162] Studies have also found that patients with the G allele may need higher doses of opioids to achieve similar analgesia, compared to **A/A** controls.[162-164] Non-opioid analgesics may be a therapeutic option for these patients if clinically indicated. Recent clinical data suggests that OPRM1 **G** allele carriers may be more likely to respond to naltrexone for the treatment of alcohol use disorders.[169,171]

Glutamate Receptor Kainate 1 (GRIK1) [173-177]

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 topiramate.[172-176] A polymorphism in *GRIK1*, specifically **C/C** homozygotes, has been associated with improved topiramate response for alcohol abuse.[172-176] However, the exact mechanism by which the **C** allele moderates this effect remains undetermined.[175] Topiramate may be used for alcohol dependence/abuse in patients with the **C/C** genotype where clinically indicated.

Pharmacokinetic Genes

Cytochrome P450 (CYP450) [7,72,178-269]

CYP450s are a family of hepatic enzymes that catalyze the breakdown of various substances.[180-183] **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.[7,178-269] For **CYP1A2**, **CYP2B6**, **CYP2C9**, **CYP2C19** and **CYP2D6**, patients with normal rates of drug metabolism are extensive metabolizers (**EM**). Patients exhibiting the intermediate metabolizer (**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.[186,198,221-222,226,233-234,249] The ultra-rapid metabolizer (**UM**) phenotype (high/fast activity) may lead to elevated enzyme activity, resulting in increased risk for subtherapeutic drug serum levels, poor efficacy and adverse events associated with

metabolite buildup; increased doses of medications metabolized by these systems may be clinically appropriate.[186,198,221-222,226,233,234-240]

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.[178-269] 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** activity.[189-197,201,204] The presence of this variant may increase the metabolism of a drug **in the presence of inducers** such as marijuana or tobacco smoke, as well as other medications[190-197] (see the Genecept Assay Report Interpretation Guide 2.0 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 subtherapeutic drug serum levels, poor efficacy and adverse events associated with metabolite buildup; increased doses of medications metabolized by this system may be clinically appropriate.[180,183,186,207] 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.[180,183,186,207]

The Genecept Assay® Panel at a glance

This table is for informational purposes only. Full lab results include reference to published literature.

	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; SNRIs or non-SSRI antidepressants 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	Metformin, lorcaserin or other anti-obesity therapies may be used to mitigate 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; Metformin, lorcaserin or other anti-obesity therapies may be used to mitigate weight gain if clinically indicated
	Dopamine 2 Receptor (DRD2)	Receptor affected by dopamine in the brain	Blocked by antipsychotic medications and is associated with risk for non-response/weight gain; Associated with higher risk of opioid abuse	Use caution with antipsychotics and opioids
	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 stimulants, COMT inhibitors and/or TMS may be used if clinically indicated for **Val/Val patients** Use caution with dopaminergic stimulants. Atypical antipsychotics may be used for psychotic-related disorders if clinically indicated 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) • **A1298C** • **C677T**	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
	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 or dosages	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	**CYP1A2, CYP2B6, CYP2C9** **CYP2C19, CYP2D6, CYP3A4/5**	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

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, though not diagnostic, describe the underlying biochemistry of presenting symptoms and adverse events, while pharmacokinetic results guide dosing decisions to optimize response. The genes analyzed by the Genecept Assay 2.0 are associated with a wide range of psychotropic medications and the assay can help 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 888.988.1888 or emailing DynacareNext@dynacare.ca.