# Medication Optimization Using Pharmacogenetic Testing and the Genomind Drug Interaction Guide (G-DIG) to Reduce Polypharmacy in a Mental Health Population

MIRB#: 01600

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Abstract

**1. Objective(s) and Hypotheses:**

Use of polypharmacy has significantly increased over the past two decades, which has unproven clinical benefit and increased the risk of drug-drug interactions and adverse side effects. Pharmacogenetic assays have the purported benefit of being able to predict response(s) to specific medication based on genetic markers. One such assay is the Genecept® Assay produced by Genomind, which detects 63 allele polymorphisms of 18 genes. In addition, Genomind has developed the Genomind Drug Interaction Guide (G-DIG), which examines drug-drug-gene interactions. This computerized decision tool for medication providers uses the genetic information from the Genecept Assay to look at the current medications being utilized to determine if there are specific drug-drug interactions that may be relevant given the individual's specific genetic test results.

The study will test the following hypotheses:

1) Use of pharmacogenetic testing and the G-DIG will reduce psychiatric polypharmacy.
2) Use of pharmacogenetic testing and the G-DIG information provided to providers will result in changes to the medication treatment plan based on the new information.
3) Use of pharmacogenetic testing and the G-DIG will improve overall clinical symptoms as measured by the CGI (secondary analyses).
4) Pharmacogenetic testing and the G-DIG will reduce healthcare costs associated with medications (secondary analyses).
5) Pharmacogenetic testing will reduce clinical symptoms of anxiety and depression and improve quality of life (secondary analyses).

**2. Research Design:**

This is a 12-week open-label, naturalistic study of the provision of pharmacogenetic testing information to both providers and patients. Veterans who have been prescribed polypharmacy and are experiencing a sub-optimal effect will be eligible for the study. Medication providers who are participating in the study as sub-investigators will refer their own patients for the study. Participating subjects will sign informed consent and a sample will be obtained in order to complete the pharmacogenomic testing. Providers will utilize the pharmacogenetic assay results along with the G-DIG tool to design an optimized medication regime. The overall global level of symptoms and other patient symptoms measures will be administered at baseline, 6-weeks, and 12-weeks.

**3. Methodology**

Fifty Veterans within the VAPSHCS who are prescribed polypharmacy, as defined as five or more medications, with at least two prescribed for a mental health diagnosis, and have a sub-optimal treatment effect will be enrolled in this study. The provider's medication plans will be compared before and after the pharmacogenetic assay information is provided. Number of medications will be reviewed to determine any

reduction in polypharmacy and healthcare costs. The clinical global improvement scale (CGI) and patient assessments, including measures of depression, anxiety, PTSD, insomnia, pain, drug and alcohol use, quality of life, side effects, and medication adherence will be administered at baseline, 6-weeks, and 12-weeks.

List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| CRF | Case Report Form |
| DSMB | Data Safety Monitoring Board |
| G-DIG | Genomind Drug Interaction Guide |
| HIPAA | Health Insurance Portability & Accountability Act |
| IRB | Institutional Review Board |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PTSD | Post-Traumatic Stress Disorder |
| R&D | Research & Development |
| SAE | Serious Adverse Event |
| Sub-I | Sub Investigator |
| TBD | To Be Determined |
| VAPSHCS | VA Puget Sound Health Care System |

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## 1.0 Study Personnel

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## 2.0 Introduction

Prevalence of Polypharmacy: Use of polypharmacy has significantly increased over the past two decades. The National Ambulatory Medical Care Survey from 1996-2006 found the number of psychotropic medications has significantly increased, with a 40.1% increase in the median number of medications prescribed (Mojtabai et al., 2010). This increase is even more significant for people over the age of 65, with the same survey finding that between 2004 and 2013, polypharmacy in older adults increased 145% (from 1.50 million to 3.68 million). In developed countries, approximately 30% of individuals 65 and older are prescribed five or more medications (Qato et al., 2008).

Polypharmacy is becoming more common in mental health populations. Individuals with bipolar disorder are at increased risk with approximately 1 in 5 individuals with bipolar prescribed at least four medications (Goldberg et al., 2009). Persons with schizophrenia have been shown to be prescribed antipsychotic polypharmacy in up to 50% of cases in some settings (Barnes & Paton, 2011). Veterans with PTSD and traumatic brain injury have also been shown to be at increased risk for polypharmacy (Collett et al., 2016).

Risks Associated with Inappropriate Polypharmacy: These increases in polypharmacy increase the risk of drug-drug interactions, adverse side effects,

with unproven clinical benefit. Higher levels of antipsychotic daily doses have been associated with decrements in information processing speed and verbal memory. (Rehse et al., 2016). Higher doses of antipsychotics may in turn lead to additional adverse effects, some of which are commonly treated with anticholinergics, leading to additional adverse effects (Barnes & Paton, 2011; Minzenberg et al., 2004). Reducing polypharmacy has been shown to have clinical improvements. In a population of individuals with schizophrenia, reducing antipsychotic polypharmacy led to improvements in cognition along with reductions in symptoms (Kawai et al., 2006).

Older adults may be at particular risk for the dangers of polypharmacy. Physiological changes that occur with age alter the pharmacokinetic and pharmacodynamics responses to medications, with resulting increased risks for polypharmacy as one ages. These adverse drug events can result in poor health, disability, cognitive impairment, hospitalization, increased risk of falls, and even death (Rehse et al., 2016; Zia et al., 2015). The number of prescribed medications is the single greatest predictor of inappropriate polypharmacy (Scott et al., 2015).

Veterans with PTSD and depression with traumatic brain injury may also be a risk for polypharmacy. Veterans prescribed polypharmacy have been shown to be at increased risk for suicide related behaviors, demonstrating that this is a vulnerable population, which may particularly benefit from medication optimization (Collett et al., 2016).

Barriers to Reducing Polypharmacy: Given the risks associated with polypharmacy, one might assume that there would be considerable pressure to reduce the number of medications, however, prescribers are often reluctant to remove medications for fear of destabilizing the patient. In order to reduce polypharmacy and the risks associated with it, several researchers have proposed methods by which the current medication regimen is examined and inappropriate medications removed (Lavan et al., 2016). These methods, however, are based on medication criteria, logical assumptions, and trial and error to gain the optimal medication regimen for each individual patient.

Optimizing Treatment Utilizing Pharmacogenetic Testing: The use of pharmacogenetics in clinical practice is a burgeoning field, but one that needs more research in order to determine the clinical and cost effectiveness of the receiving the pharmacogenetic test results. Pharmacogenetic assays have the purported benefit of being able to predict response(s) to specific medication based on genetic markers, thus, being able to identify medications that cannot be effectively processed and should be avoided, along with medications that may produce more optimal results.

One such assay in current use is the Genecept® Assay (Genomind, King of Prussia, Pennsylvania). The Assay detects 60 allele polymorphisms of 18 genes,

of which 12 code for pharmacodynamic proteins, e.g., receptors, transporters, enzymes, and ion channels. The remaining 6 genes code for pharmacokinetic variants, i.e., CYP450 alleles. Using a proprietary algorithm based on clinical data, the Assay suggests treatment options which might be more or less appropriate for the specific combination of genotype and indication. A naturalistic study of the use of this assay found that 87% of patients demonstrated clinical improvement as measured by the Clinical Global Impression Scale (CGI). Patients also showed decreases in depression, anxiety, and medical side effects, along with increases in their quality of life (Brennan et al., 2014). A recent systematic review of pharmacogenetic testing for the treatment of depression found that overall there was clinical benefit associated with the pharmacogenetic testing, but results for cost effectiveness were mixed (Rosenblat et al., 2017).

In addition to the Genecept® Assay, Genomind has developed the Genomind Drug Interaction Guide (G-DIG), which examines drug-drug-gene interactions. This computerized decision tool for medication providers, uses the genetic information from the Genecept® Assay to look at the current medications being utilized to determine if there are specific drug-drug interactions that may be relevant given the individuals specific genetic test results. This tool allows providers to not only identify medications that are not recommended based on their individual genetics, but also drug-drug interactions that may become problematic. Thus, this tool provides valuable information to providers in order to develop an optimized medication plan.

In summary, polypharmacy is associated with risks of drug-drug interactions, adverse side effects, with unproven clinical benefit. Pharmacogenetic testing may be able to predict an individual's response to medications based on their individual genetic results, which may be beneficial in reducing polypharmacy by eliminating medications that are not beneficial, leading to medication optimization. These pharmacogenetic assays are new to the market and have limited research data. The use of this assay to reduce polypharmacy has never been tested.

## 3.0 Objectives

The use of polypharmacy in Veterans, especially for the treatment of PTSD and traumatic brain injury, has increased over the past two decades, exposing Veterans to risks for drug-drug interactions and adverse side effects. Use of a pharmacogenetic tool that could give providers essential information needed to optimize Veteran's medication regimen has the potential to improve Veteran health outcomes, reduce risks for adverse events, and reduce treatment utilization costs.

This project is designed to evaluate the effectiveness of pharmacogenetic testing in individuals who are prescribed psychiatric polypharmacy. The study will test the following hypotheses:

- Use of pharmacogenetic testing and the G-DIG will reduce psychiatric polypharmacy.
- Use of pharmacogenetic testing and the G-DIG information provided to providers will result in changes to the medication treatment plan based on the new information.
- Use of pharmacogenetic testing and the G-DIG will improve overall clinical symptoms as measured by the CGI (secondary analyses).
- Pharmacogenetic testing and the G-DIG will reduce healthcare costs associated with medications (secondary analyses).
- Pharmacogenetic testing will reduce clinical symptoms of anxiety and depression and improve quality of life (secondary analyses).

## 4.0 Resources and Personnel

This research study will be conducted with the VAPSHCS, American Lake Division. All procedures (consent, data collection, data analysis) take place at the VAPSHCS and all data will reside within the VAPSHCS system.

Dr. Wood, as the PI, will have overall responsibility for the conduct of the study. Dr. Starck will assist in the development of the project, data analysis, and report writing. Dr. Wood will be responsible for study coordination, data analysis and report writing. Dr. Starck will assist with project development, protocol writing, data analysis, and report writing. Laurie Maus will assist with the maintenance of regulatory documents and data management. The Study Coordinator, Elaine Nevins, will be responsible for study coordination, subject consent and study assessments, data entry, and data analysis. Additional providers within the VAPSHCS may join this study and will refer their own patients to the study. All providers involved in referring patients will be sub-investigators on the study. All individuals involved in the study will be trained to protect private health information (PHI).

Genomind, Inc. will process the genetic sample and provide access to the pharmacogenetic test results from the Genecept® Assay within the G-DIG tool for providers. No PHI will be sent to Genomind, with subjects only identified with a study number.

## 5.0 Study Procedures

## 5.1 Study Design

This is a 12-week open-label, naturalistic study of the provision of pharmacogenetic testing information to both providers and patients. Veterans who have been prescribed polypharmacy and are experiencing a sub-optimal effect will be eligible for the study. Medication providers who are participating in the study as sub-investigators will refer their own patients for the study. Eligible patients will be given the opportunity to participate in this study. Informed consent will be obtained by research staff who are not the potential participant's provider to avoid any undue pressure to participate.

If the potential participant signs consent, a cheek swab sample will be obtained in order to complete the pharmacogenomic testing. The genetic information will be sent to Genomind for processing using only a unique study number. No personal health information will be shared with the sponsor. Participants will be asked to complete a short battery of psychological measures, including measures of depression, anxiety, PTSD, insomnia, pain, drug and alcohol use, quality of life, side effects, and medication adherence (See Appendix A).

After the participant signs the consent form, they will enter a 2-week baseline period. During theses 2 weeks, the pharmacogenetic test results will be available online for providers. Prior to receiving the results, providers will draft an initial medication optimization plan without the benefit of the pharmacogenetic information. The provider will also complete a Clinical Global Impression-Severity (CGI-S) rating of overall severity of symptoms for their client, and will document the participant's primary and secondary (if any) diagnoses.

When the results of the pharmacogenetic testing are ready, providers will review results using a secure web-based program and will utilize the G-DIG tool in order to determine the optimal medication regime for the patient, based on their individual genetic profile. Genomind will provide training to all investigators prior to the study start regarding the interpretation of the pharmacological assay and the use of the G-DIG tool. Genomind representatives will be available throughout the duration of the study for consultation regarding the interpretation and implementation of the testing results. For each provider, consultation is mandatory for the first two subjects and then available as needed for further subjects. If the patient is on a medication that is not currently listed in the G-DIG, the provider with inform the sponsor, and that medication will be added to the G-DIG tool. All final decisions about changing dosage, adding medications, or removing medications will be determined by the provider.

The provider will design an optimized, individualized medication regimen for the participant and document this revised plan. All clinical decisions regarding medical treatment and making any changes to medications will be made by the treating provider and their patient. Any medications that might be recommended by the testing results but are not provided by the VA's pharmacy (not on formulary) will be noted. Providers will then contact their patients by phone, mail, and/or schedule an in-clinic appointment for the subject (this can be scheduled at the initial consent appointment) to review the pharmacogenetic assay results and implement the medication optimization plan. Any medication changes will be dispensed by the pharmacy either in person or can be sent to the participant by mail. The provider will have 2 weeks (±2 weeks) to review these results and contact the patient.

After the 2-week baseline, future appointments between the provider and the participants will be conducted consistent with treatment as usual. It is recommended that appointments around 6 and 12 weeks (within a three week buffer) be scheduled, but this is up to the discretion of the provider and the needs of the patient. The provider will complete a CGI-Improvement (CGI-I) measure at appointments within the 6 and 12 week windows, as available.

Study staff will contact the participant at 6 and 12 weeks by phone to conduct phone interviews to repeat the measures of depression, anxiety, PTSD, insomnia, pain, drug and alcohol use, quality of life, side effects, and adherence. Study staff will also complete a CGI-I assessment. Study staff collecting the participant ratings will be blind to any medication changes made until the end of the subject's participation in the study. After the 12 week assessment, study staff will review the medical record to determine changes in medications.

During the consenting process, subjects will be presented with an additional consent in order to allow researchers to add the data into a research repository. Subjects can chose whether or not to participate. If they do, their data will be entered into the repository. If they do not, their data will be kept during the time of the study and maintained as per IRB rules and regulations.

Risk/Benefit Ratio: This study naturalistic study presents only a limited risk to subjects and is associated with the possible benefits of reducing polypharmacy, improving symptoms, and reducing the risk of adverse events. Essentially, the only intervention in this study is the provision of additional data to the provider that may aid in choosing more appropriate medications.

Potential risks of this study include participants becoming uncomfortable with questions asked on the survey, potential for breach of confidentiality, and the risk that if the assay provides poor advice, a medication chosen may not have the desired effect (of course this is always a risk when prescribing any medication and is not exclusive to this study). Since this is a naturalistic study,

side effects of medication treatment are an expected part of treatment as usual and will be handled by their provider as part of their regular clinical care.

Vulnerable Populations: This is a naturalistic study, so we are interested in opening it up to a representative sample of Veterans in order to evaluate the potential benefit of receiving the pharmacogenetic test results. Since all subjects would already have been prescribed polypharmacy, providing their medication providers with information about how their body processes medications may be helpful to reducing the number of medications and potentially improving symptoms and reducing side effects. This study does not recommend the prescribing on any medication. All decisions regarding medication prescriptions will be made by the provider and the participant. Thus, vulnerable populations are at no greater risk for participating in the study, and participation may actually reduce risks of polypharmacy and the potential for adverse effects. In order to conduct this naturalistic study is it essential to enroll persons with mental health diagnoses. However, those patients who in the clinical judgment of their provider have impaired decision making capacity that may affect their ability to provide informed consent will not be enrolled into the study. In addition, those who have a guardian for health care decisions will not be enrolled in the study. Another vulnerable population is pregnant women. Requiring a pregnancy test to exclude women who are pregnant would represent an invasion of privacy since this study does not represent any known increase risk to an unborn fetus. However, as per IRB request, if a woman self-identifies as being pregnant, she will be excluded from the study.

Study Map:

| **Procedure** | Initial Consent Appointment | Baseline Period of 2 weeks | Week 6 | Week 12 |
|---|---|---|---|---|
| Consent | X | | | |
| Pharmacogenetic testing | X | | | |
| Provider documents initial medication plan | X | | | |
| Provider reviews pharmacogenetic testing and uses G-DIG tool | | X | | |
| Provider develops optimized medication plan | | X | | |
| Provider contact patient & contacts pharmacy to make medication changes as needed | | X | | |

| | | | | |
|---|---|---|---|---|
| Patient measures | X | | X | X |
| CGI | X | | X | X |
| Demographics | X | | | |
| PHQ-9 | X | | X | X |
| GAD-7 | X | | X | X |
| PCL-5 | X | | X | X |
| VR-12 | X | | X | X |
| PEG | X | | X | X |
| PSEQ | X | | X | X |
| ISI | X | | X | X |
| Drug & Alcohol Screening | X | | X | X |
| Side Effects | X | | X | X |
| Medication Adherence | X | | X | X |

Pharmacogenetic Sample: Genomind will provide the Genecept Assay® Test Kits for this study. The kits contain all of the specimen collection and shipping materials (e.g. buccal swab, FedEx shipping materials and prepaid shipping label). The biological sample will be collected by cheek swab. The de-identified sample will be sent FedEX. The sample will only be identified with a unique assay ID number, that is separate from the study ID number. All samples will be processed by Genomind and the results will be added into the G-DIG tool, which can be accessed by the provider through the Genomind Clinician Portal, a secure website maintained by Genomind. Because the assay results may provide important information that would be relevant and pertinent to more than just the psychiatric medication provider, subjects will be given the opportunity to sign a separate release of information to allow researchers to share the Genecept assay results with the subject's other medical providers who may benefit from the assay information. Providers may also provide the subject with a paper copy of the test results if clinically appropriate. The assay will be identified by the unique assay ID number, which will be separate from the study ID number. The biological sample itself will be destroyed within 90 days by Genomind. Documentation of destruction of the biological sample will be provided by Genomind at the end of the study.

## 5.2 Recruitment Methods

Mental health patients within the VA Puget Sound Health Care System who have been prescribed polypharmacy will be eligible for this study. All providers participating in the study will be sub-investigators on this trial and will refer their own patients. Informed consent will be obtained by study staff other than the patient's own provider to reduce any undue pressure on the patient to participate. Patients will be fifty Veterans treated for a mental health diagnosis by an enrolled provider, who are prescribed polypharmacy

as defined as five or more active medications, with at least two for the treatment of a mental health disorder.

Subjects will be identified and recruited by their medication provider who is participating in this study as a sub-investigator. Study staff may assist study providers in identifying potential subjects by pre-screening upcoming appointments. When a potential subject has been identified, the study provider will introduce the study to the subject at their next clinical visit and ask if they would be interested in getting more information about the study, providing them with an informational flier. If the subject is interested, a study staff member would speak to the potential subject in a private area, review the consent form, and provide an opportunity for the subject to sign consent to participate in the study.

The subject will be paid by check the amount of $20 per study visit, for a total of $60 if they complete all the visits. It is expected that the measures will take less than an hour to complete, so this payment seems appropriate for the amount of time requested of the participant. Checks will be mailed from the VA R&D to the subject's home.

### 5.3 Informed Consent Procedures

If a potential subject expresses interest in learning more about the study, a study staff member will speak to the potential subject in a private area and review the consent form. The potential subject will be encouraged to ask questions regarding the study. At the end of the discussion, potential subject will be given the opportunity to sign consent in order to participate in the study or to decline participation. Potential subjects may also take the consent form home and think about whether or not they wish to participate, however, this may mean that the provider will delay changing their medications until they decide whether or not to participate. In order to minimize any undue pressure or appearance of coercion, a subject's provider will not be the one obtaining informed consent and the consenting process will occur in a location separate from the provider.

All individuals obtaining informed consent will be trained to protect PHI and will be trained by the PI to obtain and document informed consent. Subjects with a legally authorized representative who are not competent to sign consent will not be allowed into the study.

During the consenting process, potential participants will also be given the opportunity to consent to have their data entered into the mental health repository (MIRB#: 00696) and stored indefinitely. This will be handled with a separate consent. Participants do not have to sign this additional consent to participate.

## 5.4 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Currently receiving outpatient treatment for a mental health diagnosis within the VA Puget Sound Health Care System from a provider who is a sub-investigator on this study.

2. Currently experiencing a sub-optimal medication response as assessed by either continued symptoms or medication side effects, which in the opinion of their treating provider would indicate a change in medications would be warranted.

3. Currently prescribed polypharmacy, as defined as five or more medications, with at least two being for a mental health diagnosis. Also allowable would be one medication for a mental health diagnosis and another medication for side effects related to a medication prescribed for the mental health diagnosis.

4. Between the ages of 18 and 75.

Exclusion Criteria

1. Any mental or physical health diagnosis, which in the opinion of their treating prescriber would prevent them from being compliant on a medication regimen or being able to complete the study measures.

2. Current/active diagnosis of severe alcohol or drug use disorder.

3. Serious medical or mental health symptoms requiring immediate stabilization and/or hospitalization.

4. Impaired decision making capacity that in the clinical judgement of their provider would affect their ability to provide informed consent.

5. Self-identification as being currently pregnant.

## 5.5 Study Evaluations

Measures:
The primary measure to determine clinical effectiveness is the Clinical Global Improvement Scale. This scale will be completed both by the provider and the study coordinator (or study personnel collecting the assessment measures).

The number of medications and treatment utilization will be collected by chart review of the subject's medical record at baseline and at 12 weeks to determine any change in the number and type of medications prescribed.

Any differences between the initial medication plan developed by the provider prior to receiving the pharmacogenetic assay results, the medication optimization plan developed by the provider after the use of the G-DIG tool, and actual clinical practice will be noted. The number and cost of medication changes will also be evaluated.

Participant assessments administered at baseline, 6 and 12 weeks will include measures from the Behavioral Health Lab (BHL; Oslin et al., 2006). These measures will include a demographic questionnaire, GAD-7 (Anxiety), PHQ-9 (Depression), PCL-5 (PTSD), Insomnia Severity Index, Chronic Pain, Screening for Alcohol and Drug use, RAND Health Survey, and Side Effects and Adherence (See Appendix A). The results of the BHL assessments will be placed into the subject's medical record. Participants will also be asked about smoking.

## 5.6 Data Analysis

Analysis Plan and Power Calculations: The primary and secondary hypotheses will be calculated using within group t-tests using the Statistical Package for the Social Sciences (SPSS). A statistical power analysis was performed for sample size estimation. The effect size was estimated to be medium (0.50) using Cohen's (1988) criteria. With an alpha = .05 and power = 0.80, the projected sample size needed with this effect size is approximately N = 34 to conduct a single sample t-test. Thus, our proposed sample size of N = 50 should be more than adequate to analyze the main hypothesis for this study and should also allow for expected attrition and the analysis of our secondary hypotheses.

Interpretation**:** Interpretation of these hypotheses should demonstrate whether the Genecept® Assay and the G-DIG tool are beneficial to Veteran prescribed polypharmacy in order to reduce polypharmacy and improve clinical symptoms. The primary limitation to this study is that there is no control group, so attribution of any change to the pharmacogenetic assay should be done with reservations. If this study shows promising results, future studies should include a randomized control group. Another limitation is sample size. Though with our estimated effect size, we should have power to detect significance, larger sample sizes are preferred to increase generalizability to a larger population.

## 5.7 Withdrawal of Subjects

Participants can choose at any time to cease their participation in the study by informing the study PI of their intention to do so. Any information collected up to that point will remain in the database.

## 6.0 Reporting

Since this is a naturalistic study, potential side effects to medications are an adverse event that is expected as part of treatment as usual. The study will collect information on side effects in the study measures. All concerns regarding side effects will be referred back to their treating provider for follow-up. In the case that the participant reveals an emergent mental or physical health issue, such as suicidal ideation, the participant will be treated as per clinical guidelines within the VA, and their immediate needs addressed as one would for any other clinical patient. Their provider will be contacted for intervention and follow-up as needed.

In the case of a Serious Adverse Event, these will be reported to the IRB as per current regulations. Genomind partners may also be informed. Definition of a Serious Adverse Event will follow IRB regulations and includes life-threatening situations, death, hospitalization, persistent or significant disability or incapacity, or a congenital anomaly or birth defect.

All study records will be kept with a code, not the participant's identifying information to reduce the chance of an unintended breach in confidentiality. This study includes the genetic sample sent to Genomind to conduct the genetic testing. This sample will be sent only with a study code, not the participant's name. The sample will be used only for the purposes of the study and will be destroyed within 60 days by Genomind.

## 7.0 Privacy and Confidentiality

All study records will be kept with a code, not the participant's identifying information to reduce the chance of an unintended breach in confidentiality. The data will be stored securely, and individuals not associated with the study will not have access to data. Identifying information, such as consent forms, will be kept separately from study data.

This study includes genetic samples sent to Genomind to conduct the genetic testing. This sample will be sent only with a study code, not the participant's name. The sample will be used only for the purposes of the study and will be destroyed within 60 days by Genomind. De-identified data in the form of the pharmacogenetic test results will be available to providers on a secure website maintained by Genomind. The test results will be kept indefinitely.

## 8.0 Communication Plan

Currently, the VA Puget Sound Health Care System is the only site conducting this study. Genomind will be notified of any serious adverse events, however no PHI will be shared.

## 9.0 Information Security and Data Storage/Movement

Hard copies of CRFs will be maintained in research offices at the American Lake Division of the VA Puget Sound Health Care System. Electronic data will be kept with the VAPSHCS computer system and will be restricted to allow access to only research personnel. The genetic sample sent to Genomind will be sent FedEx and will be de-identified.

After this study is closed, research data will be entered into the Mental Health Research Repository maintained by Dr. Wood for participants who have signed that additional consent. Anyone who has not signed the additional repository consent will not have their data entered into the repository, and the data will be kept as per R&D guidelines. Additionally, there are no plans to destroy the de-identified data from the Genecept Assay; the testing data will be stored indefinitely.

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## 11.0 Appendix A: Measures

Clinical Global Impression (CGI): The CGI (Guy, 1976) is a widely used measure of overall psychiatric function and improvement. It is a clinician-rated two-item measure, consisting of a 7-point scale to measure clinical global impression of psychiatric illness and clinical global improvement. The first item will be rated at baseline, and both items will be scored for all subsequent assessments.

Patient Health Questionnaire – 9 (PHQ-9): The PHQ-9 (Kroenke et al., 2001) is self-report, nine-item screening tool for depression. The tool rates the frequency of depressive symptoms based on DSM-5 criteria for major depression. The PHQ-9 has been shown to have a sensitivity of 88% and specificity of 88% for Major Depression, with a Cronbach alpha of .89 (Kroenke et al., 2001).

Generalized Anxiety Disorder Assessment (GAD-7): The GAD-7 (Spitzer et al., 2006) is a 7-item self-report measure of general anxiety. It has been shown to have a 89% sensitivity and a 82% specificity for identifying general anxiety disorder, based on DSM-5.

PTSD Checklist for DSM-5 (PCL-5): The PCL-5 (Blevins et al., 2015) is a 20-item self-report measure of PTSD symptoms based on DSM-5 criteria. It also measures the severity of symptoms on a Likert scale.

Veteran RAND 12-Item Health Survey (VR-12): The VR-12 (Kazis et al., 2004; Selim et al., 2009) is a 12-item instrument primarily used to measure health related quality of life and disease burden. The instrument summarizes both physical health and mental health influences on overall quality of life. The VR-12

was derived from the Veterans RAND 36 Item Health Survey and has been used extensively with a Veteran population.

Chronic Pain (PEG): The PEG is a three-item scale of pain, derived from the Brief Pain Inventory, and includes items of pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G). Overall, reliability of the PEG was good (0.73 and 0.89 in two samples). Construct validity for the PEG was also good for pain-specific measures (Krebs et al., 2009).

2-Item Pain Self-Efficacy Questionnaire (PSEQ): The PSEQ is a 2-item questionnaire of pain, derived from the 10-item PSEQ. The 2-item scale has shown good validity and internal consistency, and had good convergent validity (Nicholas et al., 2015).

Insomnia Severity Index (ISI) – The ISI (Bastien et al., 2001) is a brief screening of insomnia and is designed to be used as a research outcome measure. The scale in based on the DSM-IV criteria for insomnia and measures the individual's difficult with falling asleep, staying asleep, or waking early in the past two week. Additional questions ask about sleep satisfaction and the impact of their sleep problems on their quality of life.

Drug and Alcohol Screening: These brief screening tools for drug and alcohol use include questions regarding the use of alcohol in the past year and the use of drugs of abuse in their lifetime and then how often they used any drug mentioned in the past three months. This measure is included as part of the BHL (Oslin et al., 2006).

Demographic Questionnaire: A standard measure of demographic will obtain information regarding age, gender, race/ethnicity, level of education, current housing, current employment, and military service. This questionnaire also queries about smoking. These questions will be asked only once at baseline This measure is included as part of the BHL (Oslin et al., 2006).

Side Effects and Medication Adherence: participants will be queried on their actual adherence to the medications prescribed, actual dose taken, and doses skipped, will be queried. They will also be asked about common side effects and be given an opportunity to report any other side effect that they are experiencing. This measure is included as part of the BHL (Oslin et al., 2006).