PRIME Care (PRecision medicine In MEntal health Care)

Funding Agency: VA Office of Research and Development

Principal Investigator: David Oslin, MD

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Abstract

Background: In the last several years, commercial pharmacogenetic (PGx) testing for the selection of psychotropic medications has become widespread as a means of implementing "precision medicine", with some insurers electing to cover the cost of testing. These developments have put increasing pressure on the Veterans Health Administration to implement a mental health focused PGxs program, especially for treating depression, but without sufficient scientific study to support the utility of its clinical application.

Objectives: This project is designed to evaluate the utility of PGx testing in treating Major Depressive Disorder.

Methods: The project is a multi-site randomized clinical trial in which 2000 patient/provider dyads will be randomly assigned to receive the results of the PGx battery right after randomization (i.e., the intervention group) or after 6 months of treatment as usual (i.e., the delayed results group). The study will test the following primary hypotheses:

1. Veterans with major depressive disorder (MDD) whose care is guided by the results of the PGx battery (the intervention group) will have a higher rate of remission of depression than those in the delayed results group.
2. Provider/patient dyads in the intervention group will use fewer contraindicated medications or doses of medication based on established PGx criteria than the delayed results group.

The patient inclusion and exclusion criteria are designed to target a population of patients with a major depression diagnosis who are starting or switching antidepressants.

Anticipated Impact on Veteran's Healthcare: Despite the high prevalence of depression and its adverse impact on healthcare costs and life functioning, its treatment is often inadequate. As shown in several studies, to achieve remission from depression, patients and providers must be persistent and try multiple treatments until they find one that is both tolerable and effective. However, with each round of treatment, there is greater attrition from care. Replication of the results of the few PGx implementation studies that have been conducted to date suggest that PGx could enhance the treatment of MDD and provide an impetus for early diagnosis and treatment initiation, resulting in more rapid and higher rates of remission.

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Protocol Title: PRIME Care (PRecision medicine In MEntal health Care)

1.0 Study Personnel

Principal Investigator

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Conflict of Interest:
The investigators have no relationships that would be considered a conflict of interest for this project.

Executive Committee (EC) for the trial, all of whom will serve as investigators or site principal investigators.

This committee will regularly conduct an ongoing, internal critique of program activities, providing an opportunity to exchange information on the activities across the project. The EC is an interdisciplinary group with representation from genomic medicine, informatics, clinical research, laboratory medicine, pharmacy, ethics, and primary care. Monthly virtual meetings of the EC will be chaired by Drs. Oslin and Thase. Site PIs will be encouraged to participate in EC proceedings and scientific discovery. EC meetings will focus on the coordination of study activity such as recruitment and personnel issues. Members of the EC are listed below.

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- VA Palo Alto Cooperative Studies Program Coordinating Center
  Mei-Chiung Shih, PhD
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- VA Western New York Healthcare System at Buffalo
  Laura O. Wray, PhD, MPH
  Role in Project: Investigator
  Executive Director, VA Center for Integrated Healthcare
  Associate Professor, School of Medicine and Biomedical Sciences, University at Buffalo

Study management

Study management will be overseen by Drs. Oslin and the EC. The Crescenz VA Medical Center will be the coordinating center for this study. Both a regulatory and an operations coordinator will be housed at the coordinating site; they will report to the senior research coordinator and be responsible to coordinate with local sites on everyday study activities. The monthly site coordinator meeting will be run by the coordinating site research staff to discuss study progress, coordinate research efforts, communicate changes in the protocol or procedures, and discuss regulatory items. To kick off the project at each site, the Crescenz VA Medical Center hosted a 2-day trainings for site PIs and coordinators.

A monthly EC call will monitor the various activities of the trial and coordination with team members. Local site PIs will be invited to participate in the EC calls as needed.

The Coordinating site staff will be responsible to:

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- ensure that all required local site approvals are obtained;
- keep all engaged sites informed of changes to the protocol, informed consent form, and HIPAA authorization
- inform local sites of any serious adverse events (SAEs), unanticipated problems, or interim results that may impact the conduct of the study
- notify all local facility directors and local site investigators (LSI) when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the staff at the Philadelphia coordinating site).

2.0 Introduction

Genomic testing has the potential to improve patient outcomes and reduce patient care costs through personalizing medication selection. Commercial pharmacogenetic (PGx) testing for psychotropic and other medications has become widely available and is advertised as providing the means to implement "precision medicine." As a consequence, some insurers [e.g., the Centers for Medicare and Medicaid Services (CMS)] have elected to cover the cost of PGx testing. While there is evidence for this approach in other areas of medicine, clinical application to psychiatry has proceeded without sufficient scientific study. Nonetheless, the commercialization of genomic testing has led to increased pressure on the Veterans Health Administration (VHA) to implement a mental health focused PGx testing program, especially for treating depression.

While there is evidence that genetic variation affects the metabolism of psychotropic medications and, genetic testing to identify known variants has been commercialized, the clinical utility of these findings has yet to be established. Moreover, implementing such tests in routine care is complex, requiring a systematic approach to ensure efficiency, effectiveness, and an appropriate understanding of its clinical implications. To bridge the implementation gap, this project will consist of a randomized clinical trial (RCT) to evaluate the utility of PGx testing in treating Major Depressive Disorder (MDD). The program project will be known as the **PRIME Care** study. Focusing on PGxs in mental illness represents a distinct opportunity for the VA to contribute to the advancement of precision medicine in the United States, complementing the work of other federal agencies working to advance the personalized treatment of cancer, cardiovascular disease, and other medical disorders. MDD is one of the most common conditions associated with military service and combat exposure. Moreover, MDD increases suicide risk and worsens the course of common medical conditions, making it a leading cause of functional impairment and mortality. Thus, validating a PGx test to personalize MDD treatment could contribute substantially to improving the healthcare of Veterans.

The multi-site RCT, involving up to 25 sites, will examine whether and how patients and providers use genetic test results at the time an antidepressant medication is initiated to treat MDD and whether use of the test results improves patient outcomes. The PGx test consists of a battery of genetic markers that principally identify genetic variation affecting the metabolism of psychotropic medications. The project will also examine patients' and providers' experience of the PGx testing; establish processes to educate patients and providers, and explore ethical and economic issues related to genetic testing. Thus, the program will empirically evaluate the utility of genetic testing for Veterans who are being treated for MDD and will facilitate the development of standards for PGx testing within the VA healthcare system (VHA). Lastly, the RCT will yield a rich data source for the discovery of new PGx testing methods and the exploration of

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approaches that combine genetic testing with other treatment response modifiers (e.g., other medications, obesity, tobacco or alcohol use).

3.0 Objectives

The design of this randomized clinical trial, which will be registered on clinicaltrials.gov, is a two-arm, 24-week, parallel-groups comparison of patient/provider dyads that will be randomly assigned to receive the results of the PGx test at the time the planned treatment is initiated (intervention group) or to have the results returned after 24 weeks of treatment as usual (delayed results group). The study will be conducted in up to 25 participating VA Medical Centers. In the intervention group, patient/provider dyads will be encouraged but not obligated to follow the recommendations resulting from the PGx battery to inform shared decision making. The primary aims and secondary aims of the trial are to *evaluate the utility of PGx testing in the treatment of MDD* and to understand how providers and patients use the information for shared treatment decision making, respectively. The study will test the following hypotheses:

1. Veterans with MDD whose care is guided by the results of the PGx battery (the intervention group) will have a higher rate of remission of depression than the delayed results group. (Primary Hypothesis)
2. Provider/patient dyads in the intervention group will use fewer medications that have potential gene-drug interactions based on commercial PGx test results than dyads in the delayed results group. (Primary Hypothesis)
3. Veterans in the intervention group will have better secondary outcomes than the delayed results group, including depressive symptom severity, side effect rate, treatment adherence rate, number of outpatient visits, and functional improvement. (Secondary Hypothesis)
4. Three months after receiving the PGx battery results, the delayed results group will show time-dependent changes in antidepressant prescribing and reductions in depressive symptoms that are similar in direction and magnitude to those seen in the intervention group. (Secondary Hypothesis)

In addition to the primary and secondary aims of the project, we have included a number of exploratory aims such as examining other outcome markers, understanding provider and patient educational needs for PGx testing, understanding the ethical implications for providing PGx testing, understanding the biological relationship of serum concentrations of medication to PGx testing, and examining other genetic markers that may predict treatment using Genome Wide Association Study (GWAS) methods. In addition, we hope to better understand the interaction between sleep and activity and antidepressant use by offering an optional actigraphy component at selected sites.

4.0 Background

Major depressive disorder – impact and treatment. We chose to focus on MDD because it is one of the most common conditions associated with military service. The high rate of MDD in military personnel is due, in part, to exposure to traumatic experiences, including witnessing combat and separation from family during deployment or military training [1]. For example, based on data collected in 2011 from a de-identified cross-sectional survey of active duty soldiers, the Army Study to Assess Risk and Resilience in Service members (Army STARRS) reported that the 30-day prevalence of MDD was 4.8%, compared to less than 1% among a

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civilian comparison group [2]. A meta-analysis of 25 epidemiological studies estimated the prevalence of current DSM-IV MDD to be 12.0% among currently deployed U.S. military personnel, 13.1% among previously deployed personnel, and 5.7% among individuals who were never deployed [3]. Among Veterans seeking care in the VHA, an estimated 21% of post-9/11 Veterans suffer from MDD, a rate similar to that of PTSD [4]. Moreover, MDD results in poor overall quality of life, decreased productivity, and increased mortality, accounting for about two-thirds of all cases of suicide [5]. Worldwide, MDD is the fourth leading cause of disease burden and is among the top five causes of morbidity [6-8]. Depression contributes to increased healthcare costs by increasing the risk for and adversely affecting the outcomes of a variety of conditions, including heart disease, which is the major cause of mortality in the United States [9-16].

The recently updated VA/DOD depression treatment guidelines recommend that either antidepressants or psychotherapy be used as a first-line treatment for mild-to-moderate depression and that a combination of these treatments be used for more severe, chronic, or recurrent depression [17]. However, beyond recognizing that several classes of newer generation antidepressants are more commonly used as first-line medications, there is no guidance as to which particular antidepressant should be prescribed or what might guide the change from one medication to another in the absence of a clinical response. In essence, the selection of antidepressants is a trial and error process based on clinical judgment and the occurrence and severity of side effects. Although antidepressants are approved by the Food and Drug Administration (FDA) to treat disorders other than MDD, they are most widely used to treat depression and thus are a natural focus for this project. A 2009-2012 survey of medication use showed that 9.0% of Americans of all ages used an antidepressant in the last 30 days, making them the second most commonly prescribed class of medications behind lipid lowering agents (12.4%) and ahead of analgesics (8.8%) [18]. Moreover, the rate of antidepressant use increases with age (15% of those over 65 took an antidepressant in the last month), which is highly relevant to an aging Veteran population. Within the VHA population, 59% of Veterans with depression (n>300,000) are actively prescribed an antidepressant (VINCI data – see appendix 1).

Despite their widespread use, antidepressants produce a relatively low remission rate in clinical practice. One of the largest community trials conducted for MDD, the Sequenced Treatment Alternatives to Relieve Depression **(**STAR*D**)** trial, demonstrated that only about one-third of patients achieved remission with the first treatment, and that the odds of remission decreased further for each successive treatment trial [19]. To achieve remission from depression, patients and providers must try multiple treatments until they find one that is both tolerable and effective [20]. A major factor limiting a medication's effectiveness is the patient's willingness to persist in care and, if necessary, try several different courses of pharmacotherapy. Indeed, the STAR*D trial showed that with each subsequent trial of an antidepressant there was an increase in patient dropout from treatment, further reducing the likelihood of effective treatment [19, 21]. These findings underscore the potential value of personalized or precision treatment, in which the first choice of a medication may yield the highest success rate and the greatest reduction in morbidity and mortality.

Using genetics to improve treatment response. Precision medicine is only possible when we rely on science, rather than trial and error, to guide the choice of treatment(s). However, treatment matching is complex and influenced by the pathophysiology of the disease, the pharmacokinetic properties of the medication, and the mechanism(s) of action of the medication, all of which may differ among individuals. In the last decade, there have been substantial efforts to match patient characteristics to treatment, particularly by identifying genetic variation that moderates the treatment response either pharmacokinetically or

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pharmacodynamically. Although non-genetic biomarkers or other characteristics can be used to match patients to specific treatments, genetic variation has been the most common focus of the burgeoning field of precision medicine.

Two common approaches have been used to implement precision medicine. The first focuses on disease variability, i.e., the fact that most disorders are heterogeneous and, as a consequence, different treatments are required for different subtypes of the disorder. The second approach focuses on the pharmacokinetics of specific medications. This approach has been used by a variety of companies to identify genetic variation affecting the metabolism of many commonly prescribed medications, including psychotropics. These companies have applied findings from some of the 140 FDA-approved medications whose labels contain PGx information, most of which affects metabolism (i.e., the drugs' pharmacokinetics). These companies classify individuals as slow, normal, rapid, or ultra-rapid metabolizers of specific groups of drugs based on the genetic variation detected in those individuals. Thus, PGx testing rests on the concept that a patient who is a slow metabolizer of a medication will have a very high level of the medication and a greater likelihood of side effects than a normal metabolizer. Further, a rapid or ultra-rapid metabolizer will need a higher dose of the medication than a normal metabolizer to ensure an effective dosage of the medication. Despite the intuitive nature of this approach, its implementation and impact on clinical outcomes are mostly untested.

Current evidence base for the PGxs of psychotropic medications. The Evidence Based Synthesis Program released a report on the use of PGx testing for antidepressants, concluding that more research was needed before routine testing could be incorporated effectively into clinical practice [22]. The just-released VA/DOD Clinical Practice Guidelines for Major Depression reached the same conclusion [17]. Despite substantial evidence that genetic variation is highly predictive of differences in the metabolism of antidepressants, there is only marginal evidence that these differences impact clinical outcomes [23, 24]. Variation in the genes encoding the hepatic CYP450 enzymes accounts for most of the variation in the metabolism of antidepressants [23], with variation in *CYP2D6* and *CYP2C19* genes affecting the metabolism of many of these drugs. The FDA encourages pharmaceutical companies to include PGx information in drug labels, which together with genetic information can be used to characterize patients as ultra-rapid, rapid, or slow metabolizers of the medications. There is also growing interest in the use of genetic variants that yield pharmacodynamic differences among drugs. Potential moderators of treatment response include variation in genes encoding serotonin receptors (e.g., 5-HT1A and 5-HTR2A, encoded by *HTR1A* and *HTR2A*), the serotonin transporter (*SLC6A4*), the dopamine transporter (*SLC6A3*) and inflammatory responses to antidepressant drugs (e.g., changes in the concentration of interleukin-1β) [25]. Thus, commercial PGx tests often combine pharmacokinetic and pharmacodynamic marker information in the algorithms that they use to make antidepressant treatment recommendations.

Three small (n's of 51-148 patients), randomized trials compared PGx-guided treatment with usual care [26-28]. Only one of the three trials showed an advantage for the guided treatment approach, i.e., a higher rate of remission and fewer sick days in treatment than unguided treatment [27]. As shown on clinicaltrials.gov, two large trials with the Assurex product are currently underway, and Assurex is collaborating with the Centre for Addiction and Mental Health (CAMH) in Toronto on a large open-label joint PGx study. Finally, one industry-sponsored trial (Pathways) (n=300), initiated in 2016, is being conducted in the VAHS. The VA study focuses on treatment refractory depression and bipolar disorder and is recruiting 3-4 subjects per month.

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Pooled results of several studies, mostly sponsored by Assurex, provide modest support for PGx testing to guide antidepressant treatment, though findings must be interpreted with caution because of the small samples and the open-label design. These studies suggest that guided treatment may result in lower health care utilization and lower pharmacy costs than unguided treatment (these outcomes will be evaluated in the current RCT in secondary analyses). The pooled findings suggest that the use of guided treatment can result in patients experiencing higher rates of remission from depression [29-31]. Open-label evidence also suggests that Assurex's proprietary algorithm for combining genetic marker data is superior to the individual use of genetic marker data [32]. Thus, the sum of the evidence shows that the combinatorial use of multiple markers may be of benefit even when the variance accounted for by some markers is small. Assurex has sought to leverage this finding by including putative pharmcodynamic markers, such as variants in serotonin receptor genes, which have much less consistent evidence to support their use individually. The identification of novel markers and alternative approaches to weighting the markers is an exploratory focus, which is linked to the current RCT. This additional source of hypothesis testing will seek to develop a more informative test that takes into account not only genetic markers, but other health care behaviors (e.g., smoking and the use of other medications that can affect antidepressant pharmacokinetics). In this manner, the PRIME Care study will yield critical information about how best to leverage PGx results to improve treatment efficacy, independent of the results from the RCT evaluating the standard delivery of PGx testing.

Presentation of results. The process of presenting genomic results to the patient and provider has not been well studied, though the evidence synthesis identified it as an important area on which to focus given its obvious clinical relevance. We include an evaluation of this process. Each company in the psychotropic medication genomics marketplace has taken a different approach to interpreting the genetic markers in their panels. Some companies (e.g., Genomind) present the "raw" results and the medication labeling information, leaving the provider to interpret these findings. Other companies (e.g., Pathways and Assurex [see appendix for an example report]) provide raw data along with color coding of medications (green, yellow, or red) to highlight the implications of the PGx results for selecting the optimal medication(s) for a given individual (see Appendix 2 for a sample report). Although providing both the raw data and a color code for medication selection gives the provider more direction, its benefit is untested.

Two additional areas that the evidence synthesis highlighted as needing further research are ethical considerations related to the return of results (e.g., how a patient's genetic variation in metabolism should impact potential titration of other medications that he or she is being prescribed) and educational issues such as the training needed for providers to effectively collaborate with their patients in the use of PGx testing for psychotropic medications.

Regulatory Concerns. The Institute of Medicine recently released a report on standardizing the use of biomarkers in healthcare [33], which raised several points that are relevant to PGx testing. Although regulation is needed to ensure that PGx testing is accurate and clinically relevant, regulations are not likely to be implemented soon by the FDA. In the absence of such regulation, the number of new PGx companies has grown rapidly, underscoring the need for oversight and accreditation of PGx laboratories to ensure high standards in testing. There currently is no clear guidance on how to interpret test results, nor is there a mechanism to communicate changes in the algorithm. Inevitably, the information about PGx testing will continue to grow, and the interpretation of the results will evolve, requiring that knowledge be translated to providers in an ongoing manner. Finally, among other recommendations is the need to address the practical issues of how results should be made available to providers in the

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electronic health record (EHR), the use of which is pervasive in medicine and well established in VHA. The Executive Committee and the Scientific Advisory Board for the current RCT will monitor these issues and weigh in on policy decisions that the VHA is considering for the implementation of PGx testing.

Insomnia and Depression: While each is disabling in its own right, insomnia is also highly comorbid with depression, a disorder affecting approximately 5-13% of Veterans. Research also suggests that roughly 67% of individuals with major depression also meet criteria for clinical insomnia [34]. The co-occurrence of insomnia and depression confers greater functional impairment, treatment resistance, likelihood of relapse, and suicidal risk [2,3] than either disorder alone[34, 35]. Indeed, a recent meta-analysis showed a 2- to 3-times greater risk of suicidal ideation, attempts, and death following attempts among depressed individuals when sleep disturbances were present compared to those without sleep disturbance [36]. Further, research on Veterans in particular has demonstrated significant relationships between sleep disturbance and suicide, indicating that the presence of sleep disturbance predicted shorter time to suicide completion than absence of sleep disturbance, controlling for mental health conditions, substance use, age, and region [37]. Later average sleep start time via actigraphy was significantly related to increased suicidality; after adjusting for depression and insomnia severity it was marginally significant. As such, there is a critical need to better understand the relationships between depression and sleep. We have the opportunity to add both sleep and daytime activity data to the project for some participants by using ActiGraphs to collect this data. These data would help us examine further the relationship between treatment, depression and activity. These data would be used in secondary analyses as an objective measure of response to depression treatment. Some studies have shown that actigraphy can be a useful means of studying activity levels and sleep patterns in patients with depression, but that additional work in this area is needed.

Significance. Despite the availability of dozens of antidepressants and psychotherapeutic approaches, the treatment of depression is often inadequate. As shown in several studies, to achieve remission from depression, patients and providers must try multiple treatments until they find one that is both tolerable and effective [20]. However, there is attrition with each round of treatment, which is additive. Thus, the promise of tailoring treatments to patients based on genetic variation could speed treatment response and reduce dependence on trial and error, thereby reducing attrition and improving satisfaction with treatment.

Validation of the results from the limited PGx implementation studies that have been conducted to date could usher in a new era in the treatment of MDD and provide an impetus for evidence-informed treatment, expanding access to effective treatments for the disorder. Alternatively, if the proposed study does not validate the available preliminary findings, it will provide a strong rationale to modify or limit testing as currently conducted and implemented, which carries a cost and healthcare burden. Even if the results of the RCT do not support the use of PGx testing at this time, the achievement of the other aims will provide substantial insight for the future (improved) implementation of PGx testing in psychiatry based on our discovery efforts, which will yield new information to help optimize PGx panels for a variety of disorders. Finally, almost no information is available on the impact of population genetic differences on the utility of the commercially available PGx tests. Though the present RCT will not be powered statistically to detect population by medication group differences, we will provide a preliminary description of differences in PGx effects on medication response as a function of the major population (European and African ancestry) groups. We will also be collecting some preliminary data on sleep and daytime activity for some of our participants and begin examining further the relationship between treatment, depression and activity in relation to the PGx results.

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5.0 Study Procedures

5.1 Study Design

The study is a two-arm, 24-week, parallel-groups comparison of patient/provider dyads (n=2000), which will be randomly assigned to receive the results of the PGx battery at the time of randomization (i.e., the intervention group) or receive the results after 6 months of treatment as usual (i.e., the delayed results group). The genetic test results are designed to assist the patient/provider dyad in making a shared decision as to the appropriate antidepressant. There are many additional factors that can influence that decision and the provider/patient dyads are not obligated to follow the recommendations in the genetic test report but rather are encouraged to use the results to inform shared decision making.

The study intervention. The intervention for this study is the delivery of genetic test results that reflect pharmacokinetic and pharmacodynamic effects of specified genetic markers. The choice and dose of the antidepressant to be prescribed to each patient is left to the provider and patient, though we will recommend to the provider that he or she carefully consider the genetic test results prior to selecting a medication and dose. For the trial, we will use the commercially available GeneSight™ psychotropic panel from Assurex Health. This product, which combines genetic markers related to pharmacokinetics and pharmacodynamics, has the greatest market penetration of any genetic tests for MDD treatment.

The results of the test will be available on a secure website hosted by Assurex Health and accessible by study staff and prescribing provider participants. Reports will be labeled with the participant's sample acquisition ID number, study site, provider name, participant's date of birth and initials, and date of collection. Reports will be accessed by the coordinating center and/or site study coordinators and sent directly to the prescriber via encrypted email or printed and hand delivered based on provider preference. The provider may also access the test themselves. The results will also be uploaded into CPRS via VISTA imaging. The results will be presented in the report in two ways. First, there will be a cover sheet grouping antidepressants into three color-coded categories (green, yellow, or red), which help to interpret the test results. Medications in green ("Go") have no relevant genetic interaction. Medications in red ("Stop") should be used with caution, as the patient may have either pharmacokinetic or pharmacodynamic variants that are relevant to the medication. Those in yellow ("Caution") may be at some risk of genetic interaction, but implications are not as straightforward as those in red. In addition to the interpretive results, the provider is also given the individual genetic marker information (see appendix for a sample report). Note that the genetic results will be returned to the delayed-results arm six months after randomization and completion of the 24-week assessment.

Patient Education. Patients will have access to a number of educational materials available for providers to assist in partnering with patients in the decision process. At the time of randomization, an instruction sheet will be provided to the patient that reminds them of the arm they were assigned. In the intervention arm, this instruction sheet includes a reminder to call their provider if they haven't heard back within 10 business days so that medication can be started. Educational resources also include brochures about the test result, and access to Assurex's website which is publicly available. A short whiteboard video will also be developed and available on the study website available to the public that explains the genetic test. In addition, patients have access to Assurex's call center (toll free) which will review results with

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patients at their request. This is voluntary and only initiated by the Veteran. The call number is printed on the test result along with the subject's sample acquisition ID number that allows the company's call center to identify the Veteran. This optional service is a standard part of Assurex's product.

There are no study medications prescribed as part of this study. The antidepressants used will be limited to those prescribed by an authorized VA provider and only informed by the genetic results in the intervention arm. The genetic testing is not regulated under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) process.

Provider Education. Providers will have access to a number of educational materials. These include a prerecorded "grand rounds" presentation, the slide deck for the "grand rounds" presentation that can be used locally by the local site investigator, brochures about the test result, and a quick reference guide for study providers. They will also have access to several videos around the test itself, including how to use it and how to talk to their patients about it. These videos will be provided to the CIRB. Occasional brief newsletters will also be provided to participating providers. These newsletters will highlight study related topics of interest to this group such as recent publications about pharmacogenetics, update on project progress, and provide helpful tips related to handling pharmacogenetics results. These individual newsletters will not be submitted to the CIRB. In addition, providers will have access to Assurex's website which is publicly available as well as to Assurex's call center which will provide an overview of any test. This optional service is a standard part of Assurex's product; to access, the provider calls and the Assurex staff will review the results and assist in interpretation.

Actigraphy Optional Add-On Study. Participants at selected sites will have access upon randomization to an optional component of the study to gather daytime and nighttime activity using an ActiGraph. Participating in this component of the study is optional and Veterans will complete an addendum to the PRIME Care study consent for this part of the project.

5.2 Recruitment Methods

Site Selection. Based on past experience, we anticipate recruitment of only 2 patient/provider dyads/month at each site in the first 6 months, with recruitment gradually increasing after that, reaching a maximal level of 3-4 patient/provider dyads/month during the last 2 years of the study. We have targeted sites that have high numbers of patients already being treated with antidepressants, sites with larger Primary Care Mental Health Integration programs, and sites that were successful in recruiting in past depression treatment studies. The plan for recruiting dyads is shown in Table 1.

Table 1. Study timeline.

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Time (Year)	FY17 Planning	FY17	FY18		FY19		FY20		FY21		FY22
	10/1/16 - 3/31/17	4/1/17 - 9/30/17	10/1/17 - 3/31/18	4/1/18 - 9/30/18	10/1/18 - 3/31/19	4/1/19- 9/30/19	10/1/19 - 3/31/20	4/1/20 - 9/30/20	10/1/20 - 3/31/21	4/1/21 - 9/30/21	10/1/21 - 3/31/22
Start up and hiring	X										
Regulatory finalization	X										
Knowledge Core (training and patient materials)	X	X	X	X	X	X	X	X			
Recruitment all sites		80	195	350	350	350	350	325			
Cumulative recruitment		80	275	625	975	1325	1675	2000			
Followup period											
GWAS and discovery											
Analysis and Dissemination											

Provider recruitment. The prescribing clinician (MD, DO, PA, PharmD, or CRNP) will be a participant in the study and will give one-time written informed consent prior to their participation and referral of subjects. Sites will be encouraged to consent all providers who are interested and have the potential to refer eligible patients. Each site will use different methods to recruit providers including the use of a recruitment flyer, presentations at staff meetings, an educational offering to introduce the study, or personal contact (emails or in person discussions). This is an important design consideration, as a typical multi-site study includes one or two providers per site. Thus, we are maximizing the external validity of the study's results by including providers who have no or limited stake in the outcomes (Hypothesis #2). As described below, we will also rely on feedback from various providers to understand the impact of the presentation of results and the requirements for educating providers and patients. In sum, though a smaller number of providers per site would reduce variability in implementing the results of the genetic test, it would also limit our understanding of the impact of widespread use of genetic testing and the range of providers' attitudes toward the utility of the PGx.

Temporal Sequence of Study Procedures. Patients will be identified by providers working in VA mental health programs and primary care settings. The prescribing provider will alert potential patients to the study and introduce interested patients to the Research Coordinator (RC) or other study staff at each site. The handoff from the provider to the study staff will be by secure electronic means, a phone call or in person. Sites are encouraged to have a back-up telephone contact plan so that someone on the research staff is always available to providers for phone access. This could be a backup RC or the LSI or a beeper or cell phone. Alternatively, if the patient wants to return for a later appointment for consent and randomization, this pathway should also be worked out locally so that no patient is left without contact or potentially doesn't receive treatment because of the study procedures. If providers are unable to contact staff, they should not delay treatment and thus should forgo subject referral. The prescribing provider will complete a referral form which includes confirmation of some inclusion and exclusion criteria and the responses to treatment decisions. Potential participants are those who are about to undergo antidepressant treatment for MDD or be switched from a current antidepressant to a new one. The study staff will describe the study to the patient and initiate the informed consent process. After consent, a brief baseline assessment will be conducted by the study staff to establish eligibility and to collect baseline data prior to randomization. We will keep track of the number of study referrals and will collect the following research data for those who do not consent: name, SSN, age, sex, race, and ethnicity. Name and SSN are tracked for those who do not consent so that research coordinators can determine if a subject has already been referred to the project (re-referral), and whether outcomes from an earlier referral impact eligibility. The design of the study will mimic

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routine clinical care, which will minimize the research burden and maximize the ecological validity of the trial. While every attempt will be made to complete the baseline visit within 60 minutes on the day of the clinical visit to allow randomization to occur rapidly and not delay prescribing, the patient will be given the option to return to the clinic on another day to give consent (e.g., to discuss potential participation with family) and complete the baseline assessment.

Eligible Veterans will be randomized to one of two groups - the "immediate results" group or the "delayed results" group. After completion of the baseline visit, the RC will contact the prescribing provider to inform him/her of the results of the randomization. Results for subjects assigned to the intervention group are in most cases returned to the subject's healthcare provider in 2-3 business days. Once the test results are available, the healthcare provider will prescribe an antidepressant medication. The healthcare provider is encouraged to share the results of the genetic testing with the subject and to use the results in selecting the medication and target dose. Occasionally shipping delays or the need for further sample testing may delay the results for up to four additional business days. If delays are identified, and the report will not be available within the expected three business days, the local site will notify the provider that the report has been delayed and provide an updated timeframe. The provider has the option to wait until the report is available or to proceed with prescribing without the genetic results. Subjects assigned to the "delayed" results group (and their providers) will be notified after the baseline. The provider and patient can then start the antidepressant of choice on the same day. Veterans excluded from study participation will continue to receive care from their referring provider.

Recruitment. We project that, after the 6-month start-up period, sites will randomize 3-4 patient/provider dyads/month. We will assist sites in developing a recruitment strategy that best fits their needs and adjust it as appropriate. We will enhance recruitment using a variety of methods, including clinical referrals, IRB-approved advertisements, and targeted recruitment using VISTA. Sites will be strongly encouraged to recruit as many prescribing providers as possible with an emphasis on including psychiatrists and primary care providers. An informational brochure (Quick Guide for providers) containing inclusion/exclusion criteria will be made available to prescribing providers. Local sites will also be able to use VISTA to view patient panels of consented providers and conduct chart reviews to determine eligibility. Local sites will pull a list of patients per provider with upcoming visits (up to 6 weeks out). Local sites will then conduct a brief chart review to check inclusion/exclusion criteria based on MH diagnoses and review current medications. If the patient is a good match for the project then the local site will alert the prescriber prior to the appointment, so that they can be considered for referral. Communication about these patients will be sent to providers using encrypted email. A paper copy can be given if requested by the provider; provider will be reminded to destroy the list using a locally approved method such as a secure document vault. If the provider is agreeable, local site staff may also approach these identified patients in the waiting room ahead of a scheduled visit to provide basic information about the study and a study brochure. When handing out the brochure, study staff will let the patient know that their provider is participating in this study and if they are interested in finding out if the study is a good match for them, they should talk to their provider. Study staff will not indicate that they have reviewed the patient's chart and that they may be eligible. Brochures may also be placed in waiting areas. We will host a regular learning collaborative with the site RC to share ideas about recruitment and to provide site-by-site recruitment progress reports.

Randomization. We will randomize patients to the intervention or delayed results arms, controlling for possible bias due to confounding by provider by using a within-provider

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randomization scheme within each site. Overall, this scheme will balance treatment conditions across known (e.g., primary care versus specialty care) and unknown (e.g., future adherent versus non-adherent status at randomization) provider characteristics. In addition, as we expect the depression severity of patients to be associated with primary versus specialty care status of the providers, stratification will also tend to balance depression severity across the intervention groups. The randomization will be based on a permuted blocks approach, with (slightly) varying block sizes to discourage "guessing" of upcoming allocations [38]. The research coordinator at each site will conduct the randomization, having been trained on the use of the system during the study initiation meeting. Within each site, the system will maintain a log of the participants randomized. Each site will also have a short list of random assignments, one list per consented provider, to be used in the event that there is a system failure at the time of randomization. The list of randomized allocations will be maintained separately from the tracking and research data, to ensure blinded assessments by the interviewers.

Subject payments. We will compensate subjects $20 for each of the first 4 telephone follow-up assessments (weeks 4, 8, 12, 18 follow-up assessments), $25 for the week 4 blood draw, and $50 for the week 24 telephone follow-up assessment. The treatment as usual group will also receive $25 for the week 36 telephone follow-up assessment. Participants opting to participate in using the wearable ActiGraph device will receive $25 if they wear the device for 85% of the days during the first four weeks. Subjects who do not attend the four week visit will still be compensated if they meet the wear requirements. After the first four weeks all subjects will be paid $5 for each additional week that they wear the device for 6 out of 7 days. If the subject uses the optional syncing process to sync their device through their smartphone they will receive ongoing payments paid out with other PRIME Care study payments. If they do not sync then the weekly payments from week 5-24 will be paid out in a lump sum at the end of study, prorated by number of completed weeks We will compensate subjects using direct deposit to the Veteran's bank account (or their designee's) or similar allowable and secure methods for sending these payments. Subjects are paid $50 to return the ActiGraph device at any time they decide to end participation. Note that depositing into the Veteran's bank account is the preferred and only mechanism for paying Veteran benefits such as transportation reimbursement so most Veterans have a bank account. Until we are able to secure another mechanism for paying at a national level, Veterans can only participate if they are willing to use a bank account.

Alternate Sequence of study procedures. When Veterans are unable to participate in a face to face visit, such as the COVID-19 pandemic preventing or otherwise limiting in person visits or a Veteran only available to participate by telehealth, we will have an alternate enrollment path available under a waiver of documentation of consent. Providers will submit referrals by encrypted email or Skype attaching the approved referral form or provide information over the phone for study staff to complete the referral form. The referral form contains patient name and last four; study staff will look up the phone number in CPRS. When referrals are received, study staff will call the Veteran to discuss the study and conduct oral consent. If the subject does not answer, a voicemail will be left using a script. The study staff will continue outreach to the subject, at minimum making three calls over the course of 5 business days after referral at differing times of day, no more than one call per day (5 calls maximum) when there has been no contact with the Veteran e.g. no return call from Veteran. If study staff are unable to contact the subject, they will contact the provider by encrypted email, Skype or phone at the end of 5 business days, to see if the provider wants to return to care as usual or continue outreach to the patient. If the subject is reached and consents, the baseline assessments will be completed. If

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eligible, a PGx cheek swab kit will be sent to the patient via UPS and the subject will be provided instructions on collecting the sample and returning by FedEx to Assurex. These instructions will also include directions to contact their primary care provider before returning the sample if they have felt any new physical symptoms of COVID-19, including loss of taste. We will also include in this package an Information Sheet with a summary of the study including consent elements and contact information. Study staff will check UPS tracking information daily to confirm that this package is received by the subject. Study staff will also schedule a call back time with the subject when the package is expected to arrive, to walk the subject through sample collection and shipping. We intend to make this process as easy as possible for the Veteran, assisting them with scheduling a FedEx pick-up at their home or providing them with the location of local FedEx drop boxes. Once the sample return is registered in the FedEx system, the Veteran will be randomized, and the provider and patient will be informed of the study arm. Participants will be compensated $25 for sample receipt. When visits are completed virtually, we will forgo collection of blood samples, as they are primarily used for secondary analyses. If the subject does not consent or is not eligible, the provider will be notified by encrypted email, Skype or by phone the same day, and alerted that they should return to standard care. Under a separate written informed consent, we plan to collect a DNA sample (blood or saliva) either at the in person four-week visit, at a later separate visit just for DNA collection, or by mail for home collection (saliva sample only). If the DNA sample is collected at a separate in person visit or at home, the participant will receive $25 in compensation.

5.3 Informed Consent Procedures

Prescribing providers (referred to as prescribers or providers) will participate as subjects in the trial and will be required to provide informed consent, as we will be collecting data about their prescribing practices. There are no exclusion criteria for prescribers. The site PI or research coordinator will begin recruitment of providers at the onset of the trial before recruitment begins. PI or research coordinator will obtain consent from prescribing providers; consent must be completed before referrals from a provider will be accepted. Providers will not be asked to sign a HIPAA form, as no health information is being collected from them. Version 4.0 of the provider consent dated 1/14/19 includes some minor changes related to transcribing and analysis of individual interviews. Participation in individual interviews is an optional component of the study. Providers consented using earlier versions of the consent, and who are invited to participate in these interviews, will receive an email explaining these changes. The changes will also be reviewed verbally at the start of the telephone interview.

Patients will be recruited through prescribers' referrals from clinical treatment programs at the individual sites. All advertising will require IRB approval. We have requested a HIPAA waiver to use VISTA to identify potentially eligible patients (those with appointments in the future who have MDD and no exclusionary diagnoses). These names can be distributed to consented prescribers to facilitate recruitment.

Once a Veteran has been referred to the study by their provider, there are two paths to consent (written consent or oral consent via a Waiver of Documentation of Consent). As feasible, patients will meet with the local research staff at each site to review the consent form and answer questions. Following resolution of any questions, patients who demonstrate an understanding of the nature of the study and consent will be asked to sign the study consent form and the HIPAA form. Subjects at selected sites will also be provided information on the option to participate in actigraphy for the collection of sleep and activity data. If the subject is interested, the local research staff will review the consent addendum for this optional activity

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and answer questions. The patient will be asked to sign this consent addendum if they are interested in participating in the actigraphy. A signed copy of all forms will be given to each patient.

When a face to face visit is not possible with the Veteran, an alternate oral consent process will be used under a Waiver of Documentation of Consent and HIPAA Waiver. All of the same elements of consent are covered, and the process includes documentation of who completed the consent and the date and time that oral consent was obtained. A consent Information Sheet will be sent to participants who complete the oral consent process. For those consented under the waiver of documentation of consent, a separate written informed consent form will be used for collection of DNA blood or saliva samples.

All local site principal investigators and research coordinators will maintain up-to-date required human subjects training certificates, including Good Clinical Practice, Privacy and HIPAA Focused Training, VA Privacy and Information Security Awareness and Rules of Behavior, and Research Compliance. The coordinating center will provide training and virtual supervision of site staff on all study procedures, including obtaining, documenting, and assurance of consent.

5.4 Inclusion/Exclusion Criteria

A total of 2000 men and women will be randomized. To reach this number, up to 250 subjects per site or a total of about 3000 subjects will be consented and screened.

Veteran subjects

Patient Inclusion Criteria. a) age 18 to 80 years, inclusive; b) PHQ-9 score ≥ 10 and a presumptive diagnosis of MDD per the prescriber; c) at least one prior treatment exposure for MDD (psychotherapy or antidepressant); d) intent to start treatment of the MDD with an antidepressant (simple dose increases will not be considered inclusionary), and e) willingness to provide signed, informed consent to participate in the study.

Patient Exclusion Criteria. a) current serious co-occurring psychiatric illness (i.e., schizophrenia, bipolar disorder, psychotic major depression, borderline or antisocial personality disorder, eating disorder; b) active alcohol or other drug use disorder; c) current use of an antipsychotic medication, methadone, buprenorphine, or naltrexone (depot or oral); d) augmentation therapy (e.g., use of two or more antidepressants at the time of randomization), (trazodone at a dosage ≤ 150 mg/day will not be considered augmentation and thus allowed); e) patients requiring urgent care or inpatient hospitalization at the time of consent; or f) currently incarcerated.

Prescribers

There is no limit on the number of prescribers that can be enrolled at each site. Sites will be encouraged to consent any prescriber who is interested in participating in the study.

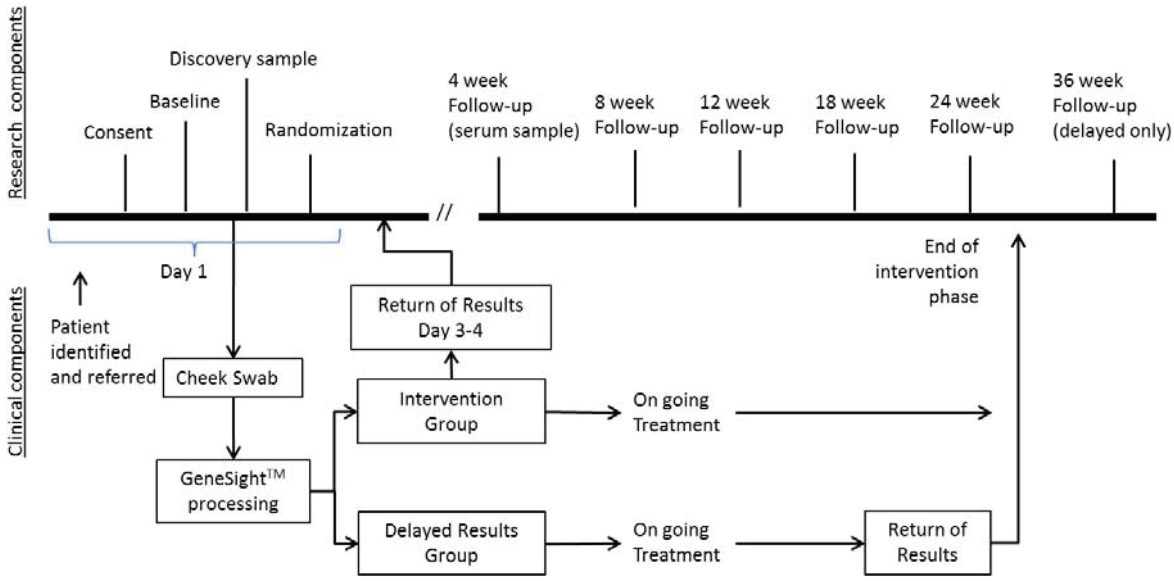
Inclusion Criteria: Capacity to prescribe
Exclusion Criteria: None

5.5 Study Evaluations

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Visit 1 (Baseline assessment). This visit will most often occur directly after informed consent has been obtained (described above). The baseline assessments and prescribing provider referral form will serve to establish the patient's eligibility. Patient-reported outcome measures (PROMs) will be collected using tablet devices/paper/or interview and entered into the Behavioral Health Lab (BHL) software based on availability of a tablet device. Responses will be populated directly to CPRS/VISTA using the VA-approved BHL software. For eligible patients, a cheek swab will be taken for the commercial genetic test and several blood samples will be taken as described below. The patient themselves or the research coordinator will collect the cheek swab, based on patient preference. Blood will be collected as part of the discovery and secondary aims as described below. Patients who consent to the optional actigraphy component (see below) will be assigned an ActiGraph device and shown how to use it, including optional syncing. Providers will record the medication that they plan to prescribe for the patient prior to randomization and rate their expectancy for treatment outcomes. After data collection and the establishment of eligibility, the patient will be randomized to the intervention group or the delayed results group. Patient/provider dyads assigned to the delayed results arm will initiate therapy with the antidepressant that the patient and provider agreed upon prior to randomization. Patients in the intervention group will have their cheek swab sample shipped for testing, with the results, in most cases, returned to the site in 2-3 business days. Prescribing will then proceed; prescribers will be encouraged to use the genetic test results in selecting a medication. Occasionally shipping delays or the need for further sample testing may delay the results for up to four additional business days. If delays are identified, and the report will not be available within the expected three business days, the local site will notify the provider that the report has been delayed and provide an updated timeframe. The provider has the option to wait until the report is available or to proceed with prescribing without the genetic results.
Visit 1 alternate. When a face to face visit is not possible, we will use an alternate virtual process for visit 1. If the subject is reached and consents to the study, the baseline assessments will be completed. If eligible, a PGx cheek swab kit will be sent to the patient via UPS and the subject will be provided instructions on collecting the sample and returning by FedEx to Assurex. These instructions will also include directions to contact their primary care provider before returning the sample if they have felt any new physical symptoms of COVID-19, including loss of taste. We will also include in this package an Information Sheet with a summary of the study including consent elements and contact information. Study staff will check UPS tracking information daily to confirm that this package is received by the subject. Study staff will also schedule a call back time with the subject when the package is expected to arrive, to walk the subject through sample collection and shipping. We intend to make this process as easy as possible for the Veteran, assisting them with scheduling a FedEx pick-up at their home or providing them with the location of local FedEx drop boxes Once the sample return is registered in the FedEx system, the Veteran will be randomized, and the provider and patient will be informed of the study arm. To encourage return of samples, participants will be compensated $25 for sample receipt. If the sample is not registered in the FedEx system within 10 business days of referral, the provider will be notified by the study staff so that they can determine whether to return to usual care or to continue. Blood draws are not included in this virtual visit.

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Visits 2-6 (Weeks 4, 8, 12, 18, and 24). During treatment, patients will be assessed by centralized assessment center personnel (at the Crescenz VAMC), with all follow-up assessments conducted by telephone. The outcomes assessors will be blinded to the study arm. At each telephone visit, patients' depressive symptoms, medication adherence, and side effects will be assessed. For those participating in the ActiGraph component, we will also ask about their use of the ActiGraph and any problems they have encountered with the device. Support will be provided as needed. At 36 weeks, we will repeat a final assessment in the delayed results group to test Hypothesis #4 (i.e., that they will ultimately show changes in antidepressant prescribing and reductions in depressive symptoms that are similar in direction and magnitude to those seen in the group that received genetic test results at the outset of the trial). We chose to administer the assessments by telephone centrally because centralized assessment helps to maintain the masking of the treatment condition; enhances consistency in the assessments; allows the use of standardized methods to reach patients, thereby reducing the amount of missing data; and reduces cost. Our group has considerable experience in administering self-assessment instruments by telephone [39, 40]. Outreach efforts will include varying call attempts at different times of the day with one attempt in the evening or on a Saturday, sending a letter, and reaching out to the participant's respective VA site to see whether there is new/additional contact information. Our practice is to call twice, send a letter and then follow with a third call unless instructed differently by the Veteran. We will continue to call up to five times.

At visit 2 we will also collect three different blood samples for the serum antidepressant level, mRNA assay, and serotonin assay. The local research coordinator will contact the subjects to arrange for the blood draw and will report back to the coordinating site when this is accomplished. The blood draw and visit 2 interview will be coordinated to ideally occur within 7 days of each other. We expect some participants to miss visits and/or drop out of the follow-up calls. If not collected at baseline for any reason or the sample was not viable, DNA is also collected at this visit if written informed consent has been obtained. If subject was consented for the project under the waiver of written consent, they will be asked to sign a separate written informed consent prior to the DNA blood draw or saliva sample collection. Missing data will not be considered a protocol deviation.

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Visit 2 alternate. If the visit 2 cannot be completed in a face to face visit, the four-week assessments will be completed virtually. In these cases, the four-week blood draw will not be collected.

DNA alternate. If the 4-week visit is conducted by phone, we may send the subject by carrier a separate written DNA collection consent form, a HIPAA form, and two saliva collection kits. Study staff will walk through the written consent over the phone and consent documents will be returned with the completed kits in a prepaid return package. If the kits are returned, but no consent forms are returned, then the samples will be destroyed. Alternatively, when possible, we may complete the consent process with the subject using the DocuSign system and send the saliva kits out by mail after the subject has consented and signed electronically. Note, DocuSign requires use of the subject's email address (covered in HIPAA waiver). The subject can also choose to do a later separate in person visit to sign consent and collect the DNA sample.

Assessments. We include measures from different sources (see Table 2 below), including provider measures, patient assessments, interview data, and EHR data.

5.5.a Provider measures.

a) Prescriber characteristics and assessment of pharmacogenetic test knowledge. For every consenting provider, we will gather basic demographics: age, sex, race, ethnicity, specialty (internist, CRNP, psychiatrist, etc.), years of practice, and the fraction of the work week that the individual dedicates to clinical care (at the start of participation). This assessment also assesses knowledge about pharmacogenetics. The opinion and knowledge questionnaire may be repeated during the latter part of the trial. We added this to the consent but will do a protocol modification with the specifics prior to implementing the follow-up survey.
b) Provider profiling. For consented providers, we will identify patients engaged in care with that provider in order to examine distribution of patient diagnoses, changes in care (utilization) and changes in prescribing patterns across the course of the study. To accomplish this, we will extract prescribing and patient utilization data from VINCI for all patients for which the provider has engaged in care during the study period or in the one year pre- and post the study. We will assess the quantity and distribution of provider antidepressant prescribing as a characteristic of their practice. We will use this information to assess how often during the study providers deviate from their prior prescribing pattern. Such deviations could indicate that the provider is attempting to adjust his or her prescribing based on results from patients randomized to the intervention, and this will be used to gauge the internal validity of the study. We will also be able to examine referral patterns in relation to the available pool of patients seen by an individual provider. This characterization of providers will be important to understand outcomes for Aim 2 of the trial. In addition, characterizing provider practices will facilitate recruitment by identifying which consented providers have higher numbers of potentially eligible patients. The provider names will be given to local sites for focused local outreach efforts, which includes one on one communication with providers and chart review of consented providers scheduled visits (protocol, page 15, Recruitment) to remind providers about patient eligibility and potential patients.
c) Referral form – there are two components on the referral form.
    a. Treatment decision. At the time of recruitment, the provider will be asked to record the antidepressant that he or she would prescribe if no genetic test information were available. This will be used to measure whether the

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provider/patient dyads in the intervention group will use fewer medications that have potential gene-drug interactions based on commercial PGx test results than dyads in the delayed results group (Hypothesis #2). The provider will also rate the likelihood that the antidepressant will be effective for the patient, the patient's anticipated degree of adherence, and how helpful the provider believes the PGx results will be in informing care for the patient.

b. Confirmation of inclusion and intent to prescribe. The referral form requests that the provider confirm the lack of serious psychiatric illness, the need for urgent treatment, and the intent to prescribe monotherapy. If we later find by administrative data that an exclusionary diagnosis has been used on a patient, this will not be considered a protocol deviation as chart extraction is not the method of confirming the exclusionary diagnoses.

d) Provider Focus groups. We will ask a subset of the sites to participate in virtual focus group interviews. We will conduct up to ten 45 minute-long (15-minute presentation, 30-minute discussion) focus groups with at least 3-5 primary care providers and/or 3-5 psychiatrists (and other specialty mental health providers) in each group. The focus groups will include a brief presentation on PGxs, including an Assurex sample report of results, and discussion about current knowledge and perceptions of PGx testing. They will provide feedback on how PGx results should be returned to providers and patients, and input on overcoming implementation barriers. All groups will be held virtually via Lync On-Line Meetings so that slides can be presented. The site PIs will encourage participation and their research coordinators will coordinate the meeting arrangements. Providers will provide written informed consent prior to participation. One consent form will serve for all components of provider participation. The focus groups will also be recorded and professionally transcribed for detailed review. Study staff will also take notes.

e) Individual interviews with providers who are participating in the RCT will be used to identify barriers and facilitators to individual uptake and use of PGx test recommendations. We will sample across sites based on the provider's rate of referral and their specialty area (primary care or psychiatry). Each individual interview will take 30-45 minutes and be recorded and professionally transcribed.

5.5.b Subject data

a) Patient measures

i. Depressive symptoms – The Patient Health Questionnaire (PHQ-9), a widely used, 9-item, self-report measure of depressive symptoms with a total score of 0-27, will be completed at each visit and will serve as the principal outcome measure for the trial [41]. The instrument rates the severity of depressive symptoms, can assist in identifying treatment goals, can be used to facilitate making a diagnosis of MDD, and can guide the choice of treatment. The results of the baseline PHQ-9 assessment will be provided to the clinical team and placed in the EHR.

ii. PTSD symptoms – The PTSD Checklist for DSM-5 (PCL-5), a 20-item self-report measure, assesses the presence and severity of PTSD symptoms [42]. Items on the PCL-5 correspond to the DSM-5 criteria for PTSD. The PCL-5 can be used to quantify and monitor PTSD symptoms over time, screen individuals for the disorder, and assist in making a provisional diagnosis of PTSD. The measure will be administered at baseline both to describe the sample and in a secondary moderator analysis of patients with MDD to differentiate them by the presence or absence of PTSD symptoms. The measure will be repeated at all follow up

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assessments. The results of the baseline PCL assessment will be placed in the EHR.

iii. Anxiety symptoms – The Generalized Anxiety Disorder – 7 (GAD-7) scale is a validated measure of anxiety symptoms that will be used as a secondary outcome measure and a potential moderator of treatment, as anxiety is known to decrease the response to treatment of MDD [43]. The measure will be administered at baseline and all follow-up assessments. The results of the baseline GAD-7 assessment will be placed in the EHR.

iv. Functional assessment – The Veterans RAND 12-item Health Survey (VR-12) is a widely used measure of quality of life [44]. The VR-12 subscales measure physical and mental functioning. The scale is a publicly available version of the MOS SF-12 instrument [45, 46]. The measure will be administered at baseline and all follow-up assessments. The results of the baseline VR-12 assessment will be placed in the EHR.

v. Alcohol use – The Timeline Follow-back (TLFB) [47] will be used to estimate past 7-day drinking at baseline and at each follow-up visit. The TLFB uses a retrospective calendar method to measure daily alcohol use. We chose a 7-day TLFB window because it is easily ascertained and provides a snapshot of recent drinking that reflects average alcohol consumption. The TLFB is the most widely used outcome measure in alcohol studies [48]. The results of the baseline TLFB assessment will be placed in the EHR.

vi. Illicit drug use – The NIDA-Modified ASSIST was adapted from the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). It was developed, validated, and published by the World Health Organization (WHO) as a screening tool for substance use [49]. This self-report questionnaire will be completed at baseline to describe the patient population. The results of the baseline ASSIST assessment will be placed in the EHR.

vii. Treatment satisfaction – We will use two questions that ask about the quality of care received and the ability to receive the services desired. The questions are adapted from the 28-item version of the Mental Health Statistics Improvement Program (MHSIP) Consumer Survey [50]. We have used these two questions for 10 years in our Primary Care Mental Health Integration (PCMHI) program. Because raters assessing satisfaction with study participation at each follow-up visit are blinded to treatment assignment, we will be unable to ask specifically about the PGx testing using the MHSIP. The measure will be done at each follow-up assessment.

viii. Receiving results – at four weeks the local research coordinator will ask if patients in the intervention group were given a copy of the results. We will ask the control group at week 36.

ix. Current smoking – At each visit, we will record the average number of cigarettes smoked daily over the past week. The results of the baseline smoking assessment will be placed in the EHR.

x. Demographics – Patient will self-report basic demographic information: sex, race, branch of military, works status, marital status, and ethnicity. We will also record the patient's birthdate, address and phone number as part of a tracking data base but these data will not be part of the analytic data set.

xi. Antidepressant adherence – This is a self-report assessment of the patient's adherence to medications during the prior week. The measure will be administered at all follow-up assessments.

xii. Structured adverse effects questionnaire – The Assessment of Side Effects is a semi-structured interview designed to assess and track the course and severity

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of adverse effects including headache, nausea or vomiting, diarrhea, constipation, and sexual dysfunction. The measure will be done at each follow-up assessment. Designations of mild, moderate, and severe will be used to grade the severity of any adverse effects. The measure will be administered at all follow-up assessments.

xiii. Treatment history – By self-report, we will obtain the lifetime information about treatment exposures including psychotherapy, and self-reported effectiveness of the most helpful treatment. This will provide information on the chronicity of depression and a proxy measure of treatment resistance. It will be obtained at baseline.

xiv. Lifetime psychiatric diagnoses – The MINI International Neuropsychiatric Interview (MINI) [51] will be used to screen for lifetime mania and psychotic symptoms, panic disorder, antisocial personality disorder, and drug and alcohol dependence. It will be administered at week 4 by the local research coordinator/ staff. If missed at the 4 week interview, the questions will be asked virtually.

xv. Nutritional assessment – by self-report we will record selected nutraceuticals and foods use that have been associated with depression and/or medication metabolism. This is not a standardized assessment but rather developed for this study. The responses will be used by the discovery core to combine with genetic data to refine analyses related to outcomes and new genetic markers.

xvi. Treatment received outside the VA – This instrument will be used to collect information on all non-VA health services received, including ER, inpatient, and outpatient care. The measure will be administered at baseline and all follow-up assessments.

xvii. Early termination information – This information will be used to identify the reasons for early termination (e.g., dissatisfaction, death, left VA care).

xviii. Suicide Assessment – The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to screen for risk of suicide. This assessment will be included at the baseline visit for all subjects and in all scheduled follow up phone calls from the central call center. The results of the C-SSRS completed at baseline will be placed in the EHR.

xix. Social Support – A short Social Support assessment will be used, as social support has been demonstrated to be related to suicidal ideation. This assessment will be included at the baseline visit for all subjects and in all scheduled follow up phone calls from the central call center. The results of the baseline Social Support assessment will be placed in the EHR

b) Biological samples - All blood samples will be collected by the local site and shipped to the coordinating site for storage.

   i) Baseline samples: At baseline the blood samples include: 2 – 8.5 ml tubes for a Genome wide association study (GWAS); 2 - 2.5 ml tubes for mRNA analysis; 1 – 10ml tube for C-reactive protein, and 1 -4ml tube for serotonin analysis.

   ii) 1 month post randomization samples: this includes 1-10 ml tube for serum drug level; 2 - 2.5 ml tubes for mRNA analysis and 1 -4ml tube for serotonin analysis.

   iii) Thus at baseline we collect 36ml and at one month post randomization we collect 19 ml.

ii. Cheek swab (at the baseline visit only) to be sent to Assurex for PGx testing. Testing kits supplied by Assurex. The oral swab will be shipped directly to Assurex under a CRADA agreement for processing and analysis. Shipping

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labels will be supplied by Assurex. Each sample will be labeled with the sample acquisition number, subject initials and date of birth, site ID, provider name, randomization outcome, and date of collection. For sample verification purposes, the sample acquisition number, along with the birthdate and subject initials will also be sent to Assurex by the coordinating center, using a VA approved encrypted email method (RMS).Once results are verified, Assurex will destroy the sample. In the rare event that the sample is not able to be processed and provide a result, we will attempt to recollect the sample from the subject.

iii. Whole blood sample or saliva sample for the GWAS sample. The blood sample will be collected in Paxgene DNA tubes that draw 8.5 ml (two tubes or a total of 17 ml). An alternate method of saliva collection will be available for collection of the GWAS sample. This saliva sample will be collected in DNA Genotek Oragene OGR-600 kits or the equivalent. The blood or saliva samples will be shipped at room temperature to the Crescenz VA Medical center for storage. At the time of the GWAS, one sample will be shipped to the West Haven VA for processing and GWAS, after which it will be destroyed. The other sample will be banked for potential future use. The samples will be labeled with the study ID number and date of draw. In the rare event that the sample is not able to be processed and provide a result, we will attempt to recollect the sample from the subject.

iv. Serum drug assay. Serum will be used to measure serum levels of selected antidepressants as an intermediate phenotype for the PGx results. A single red top serum tube (10 ml) will be collected at 1 month after randomization. The sample will be processed locally by centrifuging and then drawing off the serum. Serum will be placed in cryotubes, frozen and shipped to the Crescenz VA Medical Center for storage and inventory control. When appropriate numbers of samples have been collected, they will be shipped to the Arkansas Children's hospital for processing. All shipments will follow standard procedures for tracking and security. Each sample will be labeled with the subject study ID, and date of collection. Along with the samples a manifest with the subject ID and the subject's psychotropic medication(s) and date of draw will be provided, so the correct assay can be used on the sample. Samples will be tested in the lab of Dr. Stepan B. Melnyk at the Arkansas Children's Hospital (ACH), which is an academic affiliate of the Central Arkansas Veterans Healthcare System. Dr. Melnyk's laboratory will store the specimens until samples are analyzed and results reviewed. Once this process is complete the samples will be destroyed. Results will be returned using a VA approved encrypted email method (RMS).

v. Real-time quantitation of mRNA analyses will be performed in Central Arkansas Veterans Healthcare System [52]. Specifically, blood will be collected in PaxGene tubes (2-2.5ml) at baseline and at 1 month and mRNA will be isolated using PaxGene Blood RNA kits (Qiagen). The quality and quantity of the mRNA will be assessed using NanoDrop UV/VIS &/or Picogreen Fluorescence followed by RIN Scores generated on an Agilent 2100 Bioanalyzer. Quantitative PCR will be performed with a TaqMan 7900 System. When appropriate numbers of samples have been collected, they will be shipped to the Central Arkansas Veterans Healthcare System for processing. All shipments will follow standard procedures for tracking and security. Each sample will be labeled with the subject study ID, and date of collection.

vi. Blood for serotonin assay. Whole blood will be assayed for serotonin as an index of serotonin reuptake inhibition bioeffect. The assay used also provides results for tryptophan levels. A single 1 ml sample of blood will be collected in a plastic 4 ml EDTA serum tube at randomization and at 1 month after randomization. The

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tubes will be shipped on the day of collection to the Crescenz VA Medical Center for storage and inventory control. When appropriate numbers of samples have been collected, they will be shipped to the West Haven VAMC for serotonin assays. All shipments will follow standard procedures for tracking and security. Each sample will be labeled with the patient study ID, and date of collection.

vii. C-Reactive protein – a marker of inflammation which correlates to severity of depression and will be used as a baseline marker of severity. A single red top serum tube (10ml) will be collected at baseline. The sample will be processed locally by centrifuging and then drawing off the serum. Serum will be placed in cryotubes, frozen and shipped to the Crescenz VA Medical Center for storage and inventory control. C-reactive protein, an acute-phase reactive protein, will be measured as mg/L liter of blood from the same sample using a high-sensitivity immunoturbidimetry assay. The analysis of the samples will be done through the Crescenz VA Medical Center Clinical Laboratory. Each sample will be labeled with the subject study ID, and date of collection.

c) Optional Actigraphy: Participants at selected sites will have access upon randomization to an optional component of the study to gather daytime and nighttime activity. Participating in this component of the study is optional and Veterans will complete an addendum to the consent for this part of the project. For participating subjects, the local research staff will provide an ActiGraph wearable device (ActiGraph LLC) and charging station. The device is worn on the wrist, like a wrist watch and does show the time. The subject will be shown how to wear, and how to charge and sync the device using their smartphone. Syncing is optional but allows us to monitor more closely use and problem solve with patients who are having difficulty. Participants will be asked to wear the device at all times including sleeping but not while in water (swimming, etc.). Participants will be asked to bring the device to their four week in person visit to be synced by the coordinator using actisync software. Participants will not have access to their own data but can use the device as a watch.

   i. We will obtain the devices from ActiGraph LLC using a statement of work between the Philadelphia Research and Education Foundation (our local research non-profit - PREF) and ActiGraph LLC.

   ii. The device provides the following data points: amount of activity, estimated time in bed, estimated time out of bed, steps taken, energy expenditure, amount of sleep, awakenings, and sleep efficiency

d) Electronic health record (VINCI). Data on healthcare utilization will be obtained through VINCI for:

   i. Three time periods: 12 months prior to study entry, the duration of the study, and 12 months after the study period. These data will focus on mental health and substance abuse services received by Veterans randomized in the trial, as well as data for Veterans not enrolled in the trial who otherwise met inclusion/exclusion criteria during the same time frame.

      i) Medication use – For the main trial, we will examine medication switches and adherence to the recommendations resulting from the genetic test. These data will also be used to account for other medications that could affect the metabolism of antidepressants.

      ii) Services utilization – We will extract data related to the utilization of health care services to conduct the economic analysis and as a secondary measure of treatment outcome (Hypothesis #3).

e) Patient Tracking.

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i. Subject tracking logs – To facilitate tracking and participation, we will store in a separate data table the patient name, SSN, birthdate, address and phone number. This table will not be included in any analytic data sets. This tracking will be stored on the secure MIRECC server (\\ oitphihsmsvm200.v04.med.va.gov\Research). This is necessary for tracking and to return PGx test results.

ii. Centralized tracking – The centralized call center (Crescenz VA Medical Center) will receive information for each randomized patient, including identifiable patient information (name, SSN, address, phone number, date of birth). The call center will use REDCap and the BHL software to track follow-up assessments. The software allows patient tracking, records all call attempts, and prompts centralized staff when the next assessment is scheduled. All follow-up assessments will be entered into either REDCap or the BHL software. Both the BHL and REDCap are approved for VA use.

5.5.c Assurex data from call center.

a) Provider call information. For providers who call for assistance in interpreting test results, Assurex will keep track of the name of the provider, the general nature of the questions and the sample acquisition number of the test results reviewed.

b) Patient call information. For patients who call for assistance in interpreting test results, Assurex will keep track of the sample acquisition number of the patient and the general nature of the questions asked by the patient.

Table 2: Patient assessments

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Instrument	Patient Time	Uploaded to CPRS	Baseline	Follow-up assessments	Week 36*
PHQ-9	2 min	X	X	X	X
C-SSRS	1 min	X	X	X	X
Social Support	1 min	X	X	X	X
PCL-5	5 min	X	X	X	X
GAD-7	2 min	X	X	X	X
VR-12	5 min	X	X	X	X
TLFB (alcohol)	2 min	X	X	X	X
Modified ASSIST	2 min	X	X		
Satisfaction	1 min			X	X
Demographics	1 min	X	X		
Treatment history (self-assessment)	2 min		X		
Adherence	1 min			X	X
Side effects	1 min			X	X
Screens for psychosis, panic disorder, antisocial personality disorder, mania and diagnosis for drug and alcohol use disorders	15 min			week 4 only	
Nutritional questionnaire	3 min			week 4 only	
Receiving results	1 min			week 4 intervention arm only	X control arm
Smoking status	1 min		X	X	X
Care outside the VA	1 min		X	X	X
Biological samples (Saliva, whole blood, and serum)	5 min		X	week 4 only	
Early termination				As applicable	As applicable
VA health care utilization	EHR		X	X	X
Concurrent medication use	EHR		X	X	X
Actigraphy	Wearable 6 months		X	(Continuous)	

*Delayed results group only

Storage of data. Research material will include information obtained from consented patients and prescribers. The clinical trial will use two main data collection systems for prospectively collected data: BHL software and REDCap. Both of these data collection portals have safeguards for data entry (e.g., no out of range or otherwise invalid responses will be accepted) and form validation (e.g., logically impossible responses to different questions will not be accepted). Audit logs will record any modification to the original entry. All data collection, transfer, and storage of any identified data will be performed on the VA Intranet and thus access to the system is user based and requires maintenance of all relevant employee trainings. The system will be compliant with the guidelines described in the VA Handbooks 1200, 1605, 6300, 6500, and 6502, and with the VA IT Directive 06-2.

A brief description of each source and storage site is provided below:

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a) BHL software. The participant's self-reported responses to all questionnaires used in the clinical trial, which will cover the domains of Depression (PHQ-9), PTSD symptoms (PCL-5), Functional Assessment (RAND 12-item Health Survey – VR-12), Alcohol Use (TLFB), Illicit and Addictive Drug Use (NIDA-Modified ASSIST), and Treatment Satisfaction (two items on quality of care and ability to obtain the services desired) and Participant Tracking Information, will be collected using the Behavioral Health Lab (BHL) software system. The BHL software is a VA approved and network wide installed software package that allows patients and clinicians to collect and use patient reported outcomes and allows providers to track patients in care and to graphically display assessment reports by patient or for groups of patients. The software has been in use for more than 10 years in the VA and has the capacity to allow direct entry of self-assessments using a tablet, which then links to VISTA/CPRS. For the purposes of the trial, we will use this system of data collection for the patient reported outcomes at baseline at each site and allow the assessments to populate the local clinical record. We will also use the software to track patients and store the assessment data from the follow-up interviews (\\ oitphihsmsvm200.v04.med.va.gov\Research \BHL Software). The BHL software includes personal, identifiable data such as names and social security numbers as a mechanism to interface with VISTA/CPRS and to allow convergence of data across the data collection methods.

b) REDCap (Research Electronic Data Capture) is a web-based application for managing data acquisition during clinical research. REDCap is supported by the VA Information Resource Center and is maintained within the VA firewall so that it is only accessible on the VA intranet. REDCap will be used in this trial to supplement the BHL software and will include the Veteran response data, and provider surveys.

c) CDW: In addition to prospectively collected data, we will require administrative data from the corporate data warehouse (CDW) for both prescribers and patients. The CDW is a representation of the electronic health record. The VA Informatics and Computing Infrastructure (VINCI) is a major informatics initiative of the Department of Veterans Affairs that provides a secure, central analytic platform for conducting research and supporting clinical operations activities. The VA provides services to Veterans at over 1,400 points of care. The electronic health record system used at each point of care is known as the Veterans Information System Technology Architecture (VistA). VistA provides a longitudinal view for patients receiving care nationwide and includes diagnoses, procedures, medications, labs, physiologic measurements, and text notes and reports. Data are aggregated from individual VistA systems to the VA Corporate Data Warehouse, where they are modeled and prepared for use. We will use VINCI to access pharmacy and medical care utilization records for the 12 months prior to study entry, the duration of the study, and the 12 months after the study period. These data will focus on the mental health and substance abuse services delivered to patients and the prescribing practices of prescribers.

d) Assurex outcomes will be received regularly using a VA approved encrypted email method (RMS) or data will be uploaded to a secure Microsoft Teams SharePoint folder managed by Assurex. The data will be uploaded to and stored on secure MIRECC server space. Likewise, biological sample results, and any other source of data will also be stored on secure VA server space with assigned access as need to perform study duties.

e) ActiGraph data. Data are transmitted from the device to ActiGraph LLC's web based platform (CentrePoint Data Hub). Participants have the option of syncing the device to this platform during the 6-month period using their smartphone. Research coordinators will sync data using ActiSync software at the in person four week visit. When synced, data is deleted off the device. There is no transmission of personalized identifiable data or locations. The devices do not collect or store GPS signals. The wearable is identified by a unique device number and we will only register subjects in the data hub using site name and an assigned subject identifier. ActiGraph LLC will not have access to any PII. Data will be transmitted to the VA either as a

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download from the CentrePoint data hub, portal or using a VA approved encrypted email method (RMS). An application software system provides a secure Web API (CentrePoint API) for retrieval of subject data via HTTPS. ActiGraph LLC will not use the data for any other purposes than our specific research project, and data is to be destroyed at the end of the study.

f) Transcription Audio Files and transcripts. We will use VA approved audio recording devices. Either the VA Salt Lake City (VASLC) transcription service or the VA approved vendor, Productions Transcripts Inc., will transcribe the audio files. The VASLC has a Professional Transcription Service available to VA sites and monitored by their own IRB. The PRIME Care audio recordings to be transcribed will be labeled by the provider's unique code and saved behind the VA Firewall in PRIME Care's secure shared project folder on the VISN 4 MIRECC server \\oitphihsmsvm200.v04.med.va.gov\Research). If VASLC transcription staff are used they will be given access to a limited access sub-folder. Approved study staff will place a copy of the audio files in this folder for an approved VASLC transcriptionist to access for the purposes of transcription. If Productions Transcripts Inc. staff are used, the audio files will be submitted by a study team member using a login/password to https://client.productiontranscripts.com/ and stored on secure servers located at PhonixNAP, 3402 E. University Dr., Phoenix, AZ 85034. The transcriptionist will transcribe each interview verbatim and, depending on the vendor, either save the completed transcript in the sub-folder, or make available for download through the secure website. As completed transcripts become available, final versions will be stored on the VISN 4 MIRECC server (\\oitphihsmsvm200.v04.med.va.gov\Research) in a folder accessible by study staff only. Final transcripts are coded and will only be identified by the provider ID; any identifying information will be removed before analysis. For data analysis, temporary copies of the transcripts will be used on local servers at the Buffalo and Boston VAMCs as well as the University of Buffalo. Analytic staff at these three sites may print temporary hardcopy transcripts for qualitative analysis. When not in use these hard copy transcripts will be kept in locked file cabinets and at the end of the study will be securely discarded.

5.6 Data Analysis

Prior to data analysis, it will be necessary to create appropriate databases by combining data from BHL, CDW, and REDCap, de-identified to remove all personal or identifying information (i.e., all fields with PHI or identifiers will be removed), and kept in separate password-protected files on the VISN 4 Mental Illness, Research, Education and Clinical Center (MIRECC) server space within the VA firewall. We will merge this file with the randomization assignment database (Palo Alto Cooperative Studies database). Only this resultant data file will be used in subsequent data management and analyses, and only the Principal Investigator and research staff will have access to the data. No data will be allowed outside of the VA intranet unless by agreement to make public a de-identified analytic data set.

Data Analyses. Prior to analyses, we will compare groups on a set of characteristics to check that the randomization procedure yielded approximately balanced groups. Our primary analyses will adjust for the design variables of site and provider, using fixed and random effects, respectively. If some characteristics show marked imbalance, we will perform sensitivity analyses adjusting for them, and compare and report both sets of results. The expected distributions of our responses fall within the generalized linear models family, and we anticipate that parametric models will provide adequate fit in all cases. In all analyses, we will use standard model-checking procedures to assess the validity of our models, based on residual analyses. We will examine numerical measures of fit and graphical tests of various departures from the model based on residuals. In the event that these models provide a questionable or

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inadequate fit, the sample is large enough to allow sensitivity analyses via non-parametric analogues of the primary models.

5.6.a Patient response to treatment (Hypothesis #1). The primary outcome measures will be a set of binary indicators of remission (PHQ-9 score ≤ 5) across the intervention phase time points (weeks 4, 8, 12, 18 and 24). We will use a mixed effects logistic regression model to test the hypothesis that patients whose treatment is informed by the PGx results are more likely to be in remission than those receiving usual care. The model will have a binary indicator from the intervention group as the main explanatory variable, together with variables for time and group by time effects. The model will also include a fixed effect for site. The covariance structure of the model will take the hierarchical structure of the design into account, to accommodate nesting of repeated measures within patients, and nesting of patients within providers. Including a random intercept for provider, and correlated residuals within patient, should account for the nesting, but we will use information criteria to compare the fit of different covariance structures to ensure adequate fit. As there is particular interest in the remission rate of patients at the end of treatment, we will report a model-based comparison between the groups at the endpoint of the intervention phase.

To examine the effects of patient-level and provider-level characteristics, we will include these variables and their interactions with intervention group in the logistic regression model. For example, we will examine the effects of sex, race and ethnicity, baseline depression severity, the number of prior treatment episodes, and the effects of primary care versus specialty care, etc. We will also test for heterogeneity of the intervention effect across sites (i.e., site by treatment interactions). Analyses to assess the influence of missing data, and of adherence at the provider and patient level, are described below. Our reports will include clear descriptions of the statistical methods used and the clinical interpretations of the parameters used to test the hypotheses, with estimates, standard errors, confidence intervals and *p*-values associated with the parameters.

5.6.b. Patient and provider use of PGx results (Hypothesis #2). For each provider-patient dyad in the trial, we will use the results of the genetic test to classify each medication prescribed by the provider to that patient as green, yellow, or red, thus creating an ordinal measure for each time the provider prescribes a medication. Our primary response for Hypothesis #2 will be the correspondence between the study-period prescription for the provider-patient dyad across the randomized groups. We will compare the groups on the probability of receiving medications of the three types (red, yellow, green) using mixed effects ordinal regression model, including random intercepts for providers.

5.6.c. Secondary Responses (Hypothesis #3). We will use generalized linear regression models to evaluate secondary outcomes, using the same covariates as above: a binary indicator for intervention group, and variables for site, provider, and depression severity. Regression models will include random effects to accommodate correlations due to repeated measures and nesting of patients within providers.

Secondary analyses will include an examination of the longitudinal trajectories of PHQ-9 summaries of depression severity across the intervention phase. These models will use the overall PHQ-9 score as a response, yielding a set of continuous (possibly skewed) repeated measures. These responses will be analyzed using mixed-effects linear models (or mixed-effects gamma models, depending on the degree of skewness). We will compare the groups on functional improvement, using the mental health component of the VR-12 score, with analogous generalized linear mixed effects models appropriate to the response distribution.

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We will compare the groups on the rates of side effects that are moderate or severe. Indeed, side effects may be more plausibly related to serum antidepressant levels and thus PGx results than depressive symptoms. The data will include ordinal ratings of headache, nausea or vomiting, diarrhea, constipation, and sexual dysfunction at weeks 4, 8, 12, 18, and 24. We will use a mixed effects ordinal logistic regression model to test whether there are differences in the probabilities of moderate or severe side effects between the two intervention groups. We will compare the two groups on the number of outpatient visits per patient using a regression model for count outcomes, with a random intercept for provider to accommodate nesting pf patients within providers. We expect that a negative binomial, possibly with zero-inflation, will provide the best fit to the response distribution. We will also consider the delay in treatment in the intervention group as a potential adverse outcome if it leads to more patients not receiving treatment.

Actigraphy will be used in secondary analyses, as an objective measure of response to depression treatment. While there will not be a true baseline period of assessment (pretreatment) we will utilize the first 2 weeks of study participation as a marker of baseline activity. This is consistent with depression treatment typically taking 4-6 weeks to see objective improvements. We will then examine change in daytime activity (exercise and energy expenditure) as well as nighttime sleep (efficiency, awakenings) as markers of improvement. We will examine the relationship between these markers and self-reported symptoms and contrast improvement across the two arms. We will also be able to examine the degree to which sleep and activity are moderators of depression response. Finally, there are a number of other potential questions that could be examined. The availability of genetic data would also permit analyses examining associations between genomic variants and objectively-assessed sleep and activity phenotypes

5.6.c. Economic evaluation. There are a variety of methods and perspectives that can be used in health economic evaluations. For this proposal, we will use three methods (budget impact analysis (BIA), cost-effectiveness analysis (CEA), and Markov modeling) and one perspective (VA) for the economic evaluation of the clinical trial. BIA has become essential for developing the business case for healthcare interventions generally and health technology interventions in particular. CEA combines cost and patient outcomes into a single outcome. Markov models can use the clinical trial data to run the BIA or CEA beyond the 24-week duration of the PGx trial.

The economic evaluations described above will be conducted from the payer's perspective (VA) for the main analyses. VA costs will be assessed using Decision Support Systems (DSS) National Data Extracts, which use an activity-based cost allocation method; includes fixed direct, variable direct, and fixed indirect costs; and is the official cost managerial accounting system for the entire Department of VA. Cost estimates from the VA Health Economics Resource Center (HERC) will be used in a sensitivity analysis. Access to DSS and HERC data will be requested through VA Corporate data warehouse (CDW/VINCI) and National Data Systems (NDS). Outpatient costs for the main analysis will be organized in the following groups by primary stop code field: primary care, mental health specialty care, ancillary, physical health specialty, and other (i.e., costs that fall into none of the other categories). Outpatient VA medication costs will be assessed using VA DSS data. The cost of each prescription will be based on the drug product costs and the supplies needed to dispense the prescription according to dispensing location (centralized mail order pharmacy vs. pharmacy window). PGx intervention costs will include the cost of the PGX test and additional provider time to utilize the PGx data. Other costs for setting up the communication of PGx data to providers will be

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considered sunk costs and not included in the economic evaluation. In secondary analyses, inpatient cost and non-VA healthcare utilization costs will be added to the main analysis cost. Non-VA healthcare utilization will be collected via patient self-report and average Medicare payment rates applied.

Budget Impact Analysis. The BIA will be conducted in accordance with the guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The BIA covariates will be the same as those used in the primary analysis plus one-year pre-intervention healthcare utilization costs to control for baseline cost differences. Because total costs are likely to be non-normally distributed, we will use generalized linear models (GLMs) to estimate the effect of the intervention on total costs. To calculate the incremental treatment effect on costs, we will compute two predicted costs for each participant based on the coefficients from the GLM regressions and the covariate values for each patient. The first cost prediction will be for costs as if the subject had been randomized to the PGx arm of the study, and the second cost prediction will be for costs as if the participant had been randomized to usual care. The difference between these two cost predictions represents the incremental cost effect of the intervention for a particular participant because all covariate effects will be identical for the two estimates in a given patient. We will then average the difference between these two predicted values for each Veteran across all Veterans in the sample to generate an over marginal effect and 95% confidence interval. To estimate the budget impact, we will estimate the total 6-month cost that would be incurred by VA to deliver PGx tests to all VA patients who would be eligible for the PGx trial using the inclusion and exclusion rates. This number will be multiplied by the marginal cost difference calculated above. Sensitivity analyses will include using HERC cost data and cost range for PGx testing.

Cost-Effectiveness Analyses (CEA). The CEA will be conducted in accordance with the guidelines from the US Panel on Cost-Effectiveness in Health and Medicine. The CEA result will be a ratio with marginal cost in the numerator and marginal effectiveness in the denominator. The marginal cost component of the CEA will use the methods described for the BIA above. The effectiveness component of the ratio will be calculated using disease-specific (i.e., depression) and generic (i.e., quality-adjusted life year or QALY) outcomes. The disease-specific outcomes will be measured by calculating depression-free days from the PHQ-9 scores. Depression-free days will be calculated by using a formula now used for multiple depression severity measures where a PHQ-9 score <5 is considered depression free (score=1) and a score of 15 or more is considered fully symptomatic (score=0). Scores in between will be assigned a linear proportional value. Generic QALYs will be calculated using the Veterans RAND 12-item Health Survey (VR-12) standard gamble to QALY conversion formula. Total depression free days and QALYs will be calculated using area under the curve methods. GLM methods similar to those described above for costs will be used to calculate marginal effectiveness. Typical standard error estimation methods do not apply to incremental cost-effectiveness ratios for two reasons. First, the possibility of having zero or near zero denominators is non-negligible. Second, expenditure and effectiveness estimates are rarely independent. Therefore, we will use 1000 replications of a nonparametric bootstrap with replacement model to generate an empirical joint distribution of marginal (or incremental) costs and QALYs. We will then construct acceptability curves representing the probability of falling below incremental cost-effectiveness ratio thresholds ranging from 0 to $100 per depression free days and 0 to $100,000 per QALY.

A Markov model will be constructed to evaluate the cost-effectiveness of the use of PGx tests beyond 6 months. The cycle length for the model will be 30 days with a time horizon of one-year. The baseline model population consists of Veterans initiating antidepressant

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treatment for depression. The respective ages for the baseline model population will be derived from Veterans initiating treatment for MDD in the national VA database so that findings can be generalized to all Veterans. The model structure will be adapted from the study by Perlis et al. [53], which performed cost-effectiveness analyses using a Markov model incorporating probabilities from the multicenter STAR*D effectiveness study of depression. For this study, probabilities from the current trial will be used. Patients will enter the model with a current episode of depression. The first decision node will be whether or not PGx test data are available to the prescribing clinician. Under each study arm, we will develop a state-transition model of probabilities in which an individual patient could occupy a distinct health state, depressed (on treatment consistent with PGx test or on treatment not consistent with PGx test or off treatment), well (on treatment consistent with PGx test or on treatment not consistent with PGx test or off treatment), or death. Probabilities of remission, discontinuation, and recurrence will be drawn directly from the trial and extrapolated to one year. For remitted patients ("well"), the mortality rate will be equal to the age-gender-adjusted all-cause mortality rate from the U.S. Census. For depressed patients, we will add the rate of suicide among depressed patients to the age-gender-adjusted all-cause mortality rates of the remitted patients. Costs and utility values will be calculated as described in the section for BIA and CEA studies. For the base case analysis, we will simulate a hypothetical cohort of 10,000 patients using first-order Monte-Carlo simulation. The simulated cohort will have mean demographic characteristics consistent with MDD patients initiating treatment in the VA population nationally. We will perform both 1-way sensitivity analysis on the influential model input parameters (e.g., time horizon, remission, discontinuation, recurrent rates, drug cost, and cost of genomic test) and second order Monte-Carlo simulation by generating 100 cohorts of 10,000 patients to account for potential patient heterogeneity. Since the time-horizon is 1 year, no discounting will be applied.

5.6.d. Change in prescribing in delayed results group post-intervention (Hypothesis #4). At the conclusion of the six-month intervention phase of the trial, the genetic test results will be returned to the providers (and patients) in the treatment as usual group. We expect to see a rise in use of medication categorized as green medications after the results are returned. Thus, within the delayed results group, we will use a mixed effects ordinal response model to estimate and test a time dependent change in the probability of receiving medications of the three types (red, yellow, green) after the intervention. In addition, we will perform a bivariate analysis, combining the ordinal model with a linear model for the PHQ-9 score, to examine whether change in prescribing practice (i.e. increased prescribing of green-type medications) is related to change (i.e. an expected decline) in PHQ-9 scores.

5.6.e. Biological confirmation of effect of testing. As reviewed above, the literature on genetic variation affecting the pharmacodynamics of antidepressant treatment is sparse, and the available tests depend nearly completely on the variation associated with antidepressant pharmacokinetics, where individual variants have much greater effects. As part of the clinical trial we have included the collection of additional biological samples with several exploratory aims. First we will obtain genomewide association study (GWAS) data for the 2000 participants with MDD in the PRIME Care study. This will allow us to:

1a. Conduct a GWAS on medication response traits (daily antidepressant dose in people whose depression remits with treatment, as in the main trial: PHQ-9 score $\leq$5). We will also explore via GWAS the most common side effects observed during antidepressant treatment.

1b. Evaluate the relationship of Psychiatric Genomics Consortium (PGC)-derived depression polygenic risk score (PRS) to medication response.

1c. Develop an algorithm that takes into account not only the genetic markers in the Assurex marker panel but also those identified through GWAS (1a above) as predicting daily

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antidepressant dosage and other relevant health care behaviors (e.g., smoking, use of other medications) that can affect antidepressant pharmacokinetics).

We will also use GWAS and the Assurex testing results to examine intermediate phenotypes related to serum concentrations of medications and treatment response to:

2a. Compare GWAS and Assurex testing results against serum drug level, which could identify novel response predictors. Assuming that serum drug level mediates treatment response (an underlying assumption of all of the PGx commercial tests), this will help to identify better predictors than those currently in use. Levels will be drawn once medication dosage is stable (4 weeks from randomization).

2b. Conduct a GWAS against baseline platelet serotonin (5HT) and percentage change in serotonin level (delta5HT, an index of serotonin reuptake inhibitor bioeffect) to identify potential mediators of response.

Finally, we will compare the utility of levels of C-reactive protein (CRP), a commonly available marker of systemic inflammation, with absolute levels of mRNA for macrophage migration inhibitory factor (MIF) and interleukin 1-β (IL-1-β) as predictors of antidepressant treatment response in the PRIME Care sample. _

5.6.f. Contextual assessment of PGx testing and impact on future implementation. An important aspect of this trial will be to learn about delivering PGx testing in clinical practice. We will imply the Consolidated Framework for Implementation Research (CFIR) to structure a formative evaluation of the implementation of PGx testing [54, 55]. This aim will include the quantitate knowledge assessment as well as the focus and individual qualitative assessment of providers. Specifically, we will focus on an exploration of the current state of knowledge and perceptions of PGx testing, and findings will be used to develop provider and patient materials that can support the uptake and implementation of PGx testing. We will focus on how provider and patient beliefs and expectations of pharmacotherapy and PGx tests affect their use of the results (moderating the effects of Hypothesis #2). We anticipate that we will have sufficient diversity of sites represented to use qualitative methods to explore contextual factors within the CFIR domains of Inner and Outer Settings that will be important in preparing for a national roll-out of PGx testing. We are particularly interested in the Inner Setting context of team care (PCMHI in PACT and BHIP in specialty Mental Health [MH] settings) as it relates to the ability of individual providers to make this change in their practice.

To accomplish these aims, we will recruit a subset of sites to participate in virtual (telephone/ Lync-based) focus group interviews. We will conduct up to ten 45-minute-long (15 minute presentation, 30 minute discussion) focus groups with 3-5 prescribers each, grouped by provider type (PCPs and psychiatrists (and other specialty mental health providers)). Membership will mirror the intended eligibility for provider participants in the trial. While these groups are smaller than typical focus groups, we believe that our highly educated participants will provide rich feedback and increase the feasibility of both provider and patient recruitment by helping us to understand the common perceptions of PGx testing. These focus groups will receive a brief presentation on PGx' s, including a sample report of Assurex results, and will then discuss current knowledge and perceptions of PGx testing. They will provide input that will facilitate the RCT (e.g., How can we help prescribers recruit for the trial? What information is needed to understand and use PGx results?), and feedback on how PGx results should be returned to providers and patients. The use of focus groups at this stage is important to enable group discussion to flesh out perceptions and stimulate ideas about how PGx testing can be implemented. All groups will be held virtually via Lync On-Line Meetings so that slides can be presented.

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Finally, individual interviews with providers in the RCT will be used to identify barriers and facilitators to individual uptake and use of PGx test recommendations. We will sample across sites and providers based on the providers rate of referral and their specialty area (primary care or psychiatry) to interview up to 85 providers. Each individual interview will take 30-45 minutes and be recorded and professionally transcribed. Atlas-ti software will be used to facilitate qualitative content analysis of interview transcripts.

5.6.g. Dropout and Missing Data. At the time of enrollment, we will stress to all patients the importance of follow-up assessments, independent of treatment adherence. Despite every attempt to obtain outcome data for all patients, including those who drop out of treatment, we anticipate that there will be dropout from the study as well as intermittent missing data. To assess the sensitivity of our conclusions to missing data, we will use observed data such as baseline characteristics, intervention group, and responses obtained prior to dropout, to perform further sets of analyses. The mixed effects models described above can make use of all available responses, can accommodate the heterogeneity of response times caused by intermittent missing data, and will provide valid estimates and hypothesis tests under an assumption of "ignorable missingness," meaning that the occurrence of dropout and missing data can be predicted based on observed data. We will use extensions of these models (inverse probability weighted selection models and pattern mixture models) to examine the plausibility of the ignorable missingness assumption [56]. We will perform these analyses under a range of different prediction models and assess the sensitivity of the results.

5.6.h. Adherence. For Hypothesis #1, there are two levels of adherence to be considered. First, a provider/patient dyad in the intervention group may not use a recommended medication (this is the focus of Hypothesis #2 above) and, secondly, a patient may not actually take the medication as prescribed. We will assess adherence at the provider/patient dyad level by comparing the prescriptions that are written to the recommendations of the PGx report. We will also ascertain self-reported adherence at each assessment and will supplement with prescription data. Adherence to medication is well chronicled as an important concept in the effectiveness of treatment, yet no gold standard exists for the measurement of adherence [57, 58]. Each method has advantages and limitations. The advantage in this trial of using pharmacy records is the convenience of collection and the lack of interference with clinical practice, as this is not a standard trial with a high number of data collection time points. We will assess patients' adherence to their prescribed medication via self-report at each assessment.

To assess the sensitivity of the results of the analyses described above to non-adherence, the models described above for primary and secondary outcomes will be extended using instrumental variable approaches. Here, the instrumental variable is randomization that, under some conditions, will control for unmeasured bias (due to self-selection to adhere or not) when estimating the relative effects of the medications in those who adhere to their assigned medication. Results will use data from all patients who show various degrees of adherence as measured by the availability of medication or adherence to the PGx recommendation and will yield estimates of the intervention effects that would have been seen in a study with full adherence. For a single overall measure of adherence, we will use the methods of Nagelkerke et al. [59]; if there is sufficient within-patient variation across time in adherence, we will use the longitudinal methods of Small et al. [60]. Because adherence adjustments tend to be small and do not have a large influence on treatment comparisons, we view these as sensitivity analyses, whose main purpose is to check that estimates of effect from the primary models can be reported without explicit adjustments for adherence.

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5.6.i. Adequacy of sample size. The single primary outcome is a set of repeated binary indicators of remission from depression. As we have a single outcome, we use a Type 1 error rate of 5%. Although we expect the intervention arm to be no less efficacious than the delayed results arm, we use a two-sided test. We also assume a 20% loss to dropout, distributed evenly over time, and across the two groups. The parameters that determine power are the base rate, which is the rate of treatment success expected in the delayed results arm, and the treatment effect. The anticipated remission rate in usual care is based on results from STAR*D [19]. For the base rate, we consider rates of 20-25-30-35%, and for the treatment effect, we look at effects of 5-6-7%. The study design has patients nested within providers, so it is possible that there will be small correlations between the results for two patients of the same provider. Accounting for nesting within provider should also address the nesting within sites [61]. Our design will have approximately 200 providers, with an average of ten patients per provider. The design effect due to provider is then 1+9*r, where r is our assumed provider intra-class correlation. Our sample of size 2000 is then equivalent to an "independent patients" sample of 2000/(1+9*r). We anticipate a low ICC, on the order of r<0.05. If we assume that r=0.05, then the design effect is 1.45, and the effective sample is 1379. For a base rate of 30%, and an assumed within-patient correlation of 0.4 or lower in a compound symmetry structure, then we have 82% power for a 5% treatment effect and 92% for the same effect in an ar(1) structure, with higher power for the same 5% effect with lower base rates. For r=0.01, where we have an effective sample size of 1835, we have power in excess of 90% for 5% effects, under either covariance structure. Even with a conservative estimate of r=0.1, the design effect is 1.9, yielding more than 80% power for treatment effects of 6% or greater.

5.6.j. Data management staffing. Dr. Lynch and his staff will be responsible to coordinate the various data collection methods used in the clinical trial, and will provide support to the investigators, including site principal investigators to support additional exploratory hypotheses. In this section, we describe the methods that we will use to collect, store, and distribute data from the trial.

5.6.k. Security Awareness and Training. Security awareness starts with a request by an investigator to obtain access for his or her study personnel. To gain access to the BHL and REDCap systems, a user must first attend and pass the training/hands-on certification process. The training consists of a thorough introduction to the two systems and the policies governing their use.

5.7 Withdrawal of Subjects

Subjects and providers will be made aware that they may withdraw from this study at any time during the course of the research without penalty or loss of VA or other benefits to which they are entitled. Given that there are almost no known risks from assessing the PGx profile of a patient, and that the patient will receive usual care throughout his or her study participation, no further procedures for the orderly withdrawal or termination of participation is planned. If a subject withdraws in the control group, the test results will still be returned at the 6 month time point. Withdrawal of the provider has no impact on patient participation.

6.0 Data safety and monitoring plan (DSMP)

Data monitoring. Throughout the trial, we will use an established protocol to manage patients who experience adverse clinical outcomes. Specifically, during the follow-up outcome assessments, there will be a clinical staff member available at all times to call center staff, and patients in significant distress or who have suicidal thoughts (PHQ9 item 9 >1) will speak with a

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study clinician. The call center clinician will then initiate appropriate care, which may involve initiating a rescue or working with the local investigator to facilitate care. When clinically relevant, we will notify the local site team of the need for further follow-up of the patient. Patients who drop out of care and continue to be symptomatic will be encouraged to reconnect with their clinical team. Patients who report non-adherence to medication or report that they never received their medication will also be encouraged to call their provider. In addition, the local RC will review the chart to ensure that a prescription was written during the time between randomization and the 1 month blood draw or that a note was written indicating why a prescription wasn't written. If neither are found in the chart, the RC will email the provider altering them that the patient did not receive a prescription and query if this was intention or not. Results from the assessments will not be made available in CPRS/VISTA unless required for safety issues or those so indicated at baseline.

Safety review. The DSMP is intended to ensure the safety of research patients and the integrity of the study data. Dr. David Oslin, M.D., the Principal Investigator of this program project and Dr. Thase, will be charged with the duty to receive from sites all submitted adverse events. The individual site investigators will be responsible to report any identified serious adverse events during the recruitment phase and until the 4 week assessment and the Crescenz VAMC site will be responsible to report any adverse events identified during the outcome calls. Given that there are almost no known risks from assessing the PGx profile of a patient, it is anticipated that study-related adverse events will be low. Given that the study population will include patients with serious mental illnesses, adverse events such as hospitalization will occur, but are expected as part of the natural disease course. After assigning causality, the site investigator or the study P.I. or Co-Investigator will decide the course of action for the study patient. The site PI, or for the outcome group, the study Principal Investigator (and, in his absence, Co-investigator) will differentiate serious from non-serious adverse events. Upon discovery, all research-related deaths will be immediately and orally reported to the CIRB and the coordinating center followed by written notification within 5 working days after being made aware of the death. All local serious unanticipated (unexpected) adverse events that are related to the research will be reported to the Central IRB and coordinating center (Crescenz VAMC) within 5 working days. Unanticipated problems that represent a risk to participants and/or others will be reported to the CIRB and the coordinating center within 5 working days. Protocol deviations that substantively affect subjects' rights or safety, or potentially compromise facility human research protection will also be reported to the Central IRB and the coordinating center within 5 working days. An annual report summarizing all adverse events and unanticipated problems/protocol deviations that did not require immediate reporting will be prepared and reported to the Central IRB at the time of continuing review. All reporting requirements as detailed in the VA-CRB-SOP-114 will be followed.

7.0 Privacy and Confidentiality

All research project personnel will complete training in the protection of human research patients in accordance with the guidelines of the U.S. Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP). The study staff (PI, clinical research coordinator, etc.) will keep all study medical records (including any codes to de-identified data) under lock and key in a secure location, as required by law. Access to all electronic data and files (e.g., database, spreadsheet) containing identifiable patient information will be limited to approved users with a login. Any computer hosting such files will have a password to prevent access by unauthorized users. If data are to be exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted at strong

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encryption levels (≥128 bits for symmetric encryption (DES) and ≥1024 bits for asymmetric encryption (RSA) while en-route to the recipient.

Aggregate data from cheek swab genetic testing will be returned to the Crescenz VAMC using a VA approved encrypted email method (RMS) or data will be uploaded to a secure Microsoft Teams SharePoint folder managed by Assurex.

The analytic data set and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. Blood will not be used for the purpose of establishing cell lines. Any hard copy records associated with the study will be kept in locked offices at the clinical site. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms.

Data used for safety monitoring will include serious adverse events, dropout rates and reasons for dropout, enrollment numbers, patient interviews, medication compliance, review of symptoms, review of clinical/diagnostic test results, protocol deviations, and blinded data. If it has been determined, for any reason, that there will be a suspension of this study, the PI will suspend enrollment of new patients but continue intervention/monitoring of previously enrolled patients if it is in the best interest of those patients.

Blood or saliva and a cheek swab will be collected for DNA analysis. The information derived from the GWAS sample (i.e., the blood or saliva sample) will not be provided to the patient. While the study is open, DNA samples will be coded with a number that provides a link to the patient's identity (samples will be accessible only by the researchers and staff involved with this study). Upon completion of the study, the sample for those subjects who consent will be kept in storage indefinitely. The lab procedures for storage include a passcode-protected locked room, and secure storage freezers. All samples will be retained securely as per lab protocols.

Individual ActiGraph activity tracker data will be returned to the Crescenz VAMC using a user id/password to download through the CentrePoint web portal or using a VA approved encrypted email method (RMS) and this data will be analyzed at the Crescenz VAMC. ActiGraph will store the data using an assigned subject identifier. ActiGraph LLC will destroy the data at the end of the study. No GPS data is collected or stored. ActiGraph will not have any PII.

8.0 Communication Plan

Data availability. To facilitate manuscript writing and other dissemination activities, Dr. Lynch and his staff will create analytic data sets and place them in data share directories on the VA Intranet as approved by the CIRB. The selection of instruments for these datasets will be based on discussions with the PI and data analysts for each particular manuscript. In general, access to these datasets will be restricted to the Programmer/Analyst, Drs. Lynch and Shih, and the project investigators. Access for other users will be at the discretion of Dr. Oslin and the investigator group for the project. All proposed manuscripts must be presented and approved by the Executive Committee prior to the initiation of analyses or access to data. This also applies to the manuscripts that are planned at the outset of the study. Failure to gain approval and proceeding to publication will result in the investigator being reported to the Office of

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Research and Development and will prompt communication with the editor of the journal to which an un-authorized manuscript is submitted.

Public data set. As outlined in the Data Management and Access Plan (DMAP), de-identified data from this trial will be made publicly available after completion of the main outcome analyses.

Communication of progress and results will be the responsibility of the Executive Committee. We will target stakeholders including policymakers, legislators, healthcare providers, patients, and the scientific community. To accomplish this, we will (1) assist investigators in the preparation of scientific presentations and manuscripts for publication, (2) inform the public and policymakers of new findings through press releases and related mechanisms, and (3) facilitate dissemination to patients and healthcare providers through websites, direct to consumer marketing, and collaboration with VISN leadership, VA national leadership, and other centers. To facilitate dissemination, site principal investigators will be engaged in all scientific aspects of the project and will participate in manuscript development and dissemination. Dissemination is one of the responsibilities of centers of excellence such as the VISN 4 MIRECC. With its focus on measurement-based care and precision medicine, the VISN 4 MIRECC is well positioned to accomplish this goal.

Publication and Presentation Plans:
At this point, there are no planned presentations for the project.

9.0 Risk/Benefit:

Potential risks: Overall, the risk to prescribers and patients is minimal. Potential risks to participants in this study include:

Prescribers: As employees, there could be a perceived risk that responses to the qualitative interviews would be available to supervisors or a sense of coercion to participate. The data collected will not be made available to individual sites and only aggregate data will be published. This risk is considered minimal. Members of our team have a great deal of experience in conducting these types of interviews.

Veteran Patients: The psychological assessment includes questions of a sensitive nature in regards to the patients' psychiatric symptoms. Some patients may experience distress or discomfort when answering questions about these issues. High levels of distress during these assessments are uncommon and staff will be trained to deal with such occurrences. We have specific operating procedures that staff follows for high-risk patients, including those that report experiencing suicidal ideation.

Genetic Testing: The principal risk of genetic testing is breach of confidentiality, with sensitive information concerning the patient's genetic risk for disease becoming known. The informed consent forms will include all of the required elements of consent for genetic testing, including an explanation of the purposes of the DNA testing, a description of any benefits to the patient or others that may reasonably be expected from the DNA testing, and a statement describing the extent, if any, to which confidentiality of records/samples identifying the patient will be maintained.

Anticipated Benefits to Patients and Society: Potential benefits to patients include the acquisition of knowledge that could reduce the likelihood of exposing them to medications that

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are less appropriate for use in that patient because of their genetic features. Benefits to prescribers are the receipt of information about genetic variation, which could facilitate their selection of medication for patients in the intervention group. Benefits to society include an improved understanding of PGx and other moderators of response to antidepressant medications that will enhance their clinical utility and the process of medications development for depression and related mental health conditions.

Comparison of risks and anticipated benefits to patients and society: The risks associated with the PGx testing are minimal. Without confirming the value of PGx testing, benefits are minimal to, at most, moderate. The risk/benefit ratio thus appears favorable to the proposed intervention.

10.0 Resources and personnel

Below is a brief description of the study roles. All will have access to sensitive health information with the exception of the executive committee.

Lead Site:

Principal Investigator – Responsible for the overall conduct of the trial and fidelity to the design; oversees all aspects of the study; facilitates training of sites and communication among local sites; leads site and Executive Committee; responsible for reporting to the CIRB and the DSMB.

Investigators – Collaborate with the PI and provide back-up of responsibilities when needed. Develops study materials, including provider education.

Executive Committee (EC) – Will conduct a regular, ongoing, internal critique of the RCT, providing an opportunity to exchange information on the activities across the project. The EC is an interdisciplinary group with representation from genomic medicine, informatics, clinical research, laboratory medicine, pharmacy, ethics, and primary care. EC members are listed at beginning of this protocol.

Senior Research Coordinator – Responsible for day-to-day aspects of the project, supervises the study coordinators and research assistants (RAs) and ensures protocol adherence and research design integrity. Interfaces with data management team.

Safety Monitor - Oversees all safety aspects of the trial, including being available to assist the research assistants during outcome monitoring when they encounter patients with significant distress or with suicidal ideation.

Regulatory and Recruitment Coordinator – Responsible for all regulatory correspondence with the CIRB, maintaining regulatory records for the coordinating site, communicating with the local sites concerning all relevant correspondence, including modifications, continuing reviews, adverse events, etc. Train local site personnel to maintain local regulatory materials. Oversees all tracking of recruitment, working to keep sites on track with the recruitment goals and reporting to the PI and EC on their progress/status.

Outcome Assessment Coordinator – Supervises the outcome assessment component being conducted at the coordinating site. Oversees the RAs conducting the research follow-up telephone interviews. Provides training to the RAs and is responsible for quality control. Manages participant payments. Ensures that standard operating procedures are followed.

Research Assistants – Conduct the participant follow-up assessments via telephone. Coordinate logistics with the local sites. Complete data entry and data cleaning.

Senior Biostatistician – oversees all aspects of data collection and management. Oversees all data analyses.

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Statistician – Is responsible for data management, storage, access and analysis. Supervises data manager. Facilitates data sharing with investigators and tracks all data use during later states of the trial. Conducts the primary and secondary quantitative data analyses under supervision of the senior statistician.

Data Manager – Aggregates data from different sources and coordinates regular data extraction from VINCI and BHL. Responsible for developing and implementing all survey in REDCap. Assures data transfer is completed securely. Responsible for assuring the return of genetic tests from Assurex.

Local Sites:

Local Site PI – Responsible for implementing the study at the local site, including subject recruitment and the supervision of the local site coordinator

Local Site Coordinator – Responsible for recruitment, consenting participants, and completing baseline assessments at the local site. Communicates with local prescribers, facilitates delivery of PGx results. Facilitates collection of participant samples and their secure delivery to the sample repository. Coordinates activities with the outcome assessment group and Regulatory Coordinator at the lead site in Philadelphia.

Other:

Assurex – Commercial genetics laboratory providing genetic testing and results based on cheek swab sample from participants based on a Cooperative Research and Development Agreement (CRADA) between the Corporal Michael J. Crescenz VA Medical Center and ASSUREX HEALTH, INC., executed 10/10/2016. Samples received by Assurex will be labeled with the sample acquisition number, subject initials and date of birth, site ID, provider name, randomization outcome, and date of collection.

ActiGraph LLC – Commercial company that provides Bluetooth Smart actigraphy monitors, in conjunction with a cloud-based Centre-Point Study Admin Portal software platform, delivering high quality, customized physical activity and sleep/wake measures while offering the data management and administrative support essential for complex, multi-site clinical research studies. A Statement of Work will cover a Master Services Agreement between the VA and ActiGraph LLC. Data received by ActiGraph will be identified only by a subject identifier and date of collection.

Janssen Research & Development, LLC, a pharmaceutical division of Johnson & Johnson – Commercial company that is providing funding though the Philadelphia Research and Education Foundation for the VA to add ActiGraphs to the PRIME Care Project. A CRADA is in place between Janssen Research & Development, LLC and the VA. Janssen Research & Development, LLC will only receive de-identified data from the project.

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