A three-arm, parallel group, multicentre, double-blind, randomized controlled trial evaluating the impact of GeneSight Psychotropic and Enhanced-GeneSight Psychotropic, on response to psychotropic treatment in outpatients suffering from a major depressive disorder (MDD) and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GeneSight Psychotropic

Short Title: Pharmacogenomic Decision Support with GeneSight Psychotropic to Guide the Treatment of Major Depressive Disorder

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PRINCIPAL SITE INVESTIGATOR SIGNATURE PAGE

Investigator name: _____

Signature: _____ **Date:** _____

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Research Ethics Board (REB) procedures, instructions from Assurex Health representatives, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices Guidelines, and national/local regulations governing the conduct of clinical studies.

The signature also confirms that the Investigator agrees that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

1.0 SYNOPSIS

1.1 Study Title

A three-arm, parallel group, multicentre, double-blind, randomized controlled trial evaluating the impact of GeneSight Psychotropic (GEN) and Enhanced-GeneSight Psychotropic (E-GEN), on response to psychotropic treatment in outpatients suffering from a major depressive disorder (MDD) and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GEN.

1.2 Objectives

The first primary objective of this study is to compare the efficacy of GEN to treatment as usual (TAU) in improving response to psychotropic treatment in outpatients suffering from a major depressive disorder (MDD) and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GEN.

The second primary objective for this study is to validate the clinical utility of the new Centre for Addiction and Mental Health (CAMH) markers and demonstrate the superior predictive capabilities of E-GEN as compared to GEN.

1.3 Interventions and Duration

Patient DNA will be collected for all participants and measured for variations in drug target genes and in drug metabolizing genes. Subsequently, recommendations for optimal choices and dose adjustments for the 33 most commonly prescribed antidepressant and antipsychotic medications will be provided to participants randomized to the GEN arm. This pharmacogenomics-based interpretive report will be provided to treating clinicians of patients in the GEN arm of the study, allowing clinicians to use the report to support their treatment decisions.

The E-GEN test incorporates into the existing GEN product new markers patented by CAMH and licensed by Assurex that are predictive of side effect of antipsychotic-induced weight gain (AIWG). The pharmacogenomics-based interpretive report from E-GEN will also be provided to treating clinicians of patients in the E-GEN arm of the study, allowing clinicians to use the report to support their treatment decisions.

Participants randomized to the TAU arm will also require collection of patient DNA. A pharmacogenomics-based interpretive report will again be generated from GEN, however, this report is not provided to the treating clinician until up to 28 days prior to the completion at 12 months of the study at which point the report will be provided to the participant. Therefore, patients in this arm will receive clinical treatment as usual, without the use or knowledge of pharmacogenetics results by their treating clinicians.

Research evaluation visits for all three arms will be completed at baseline, 4, 8 and 12 weeks. To capture long-term information, including comparison between GEN and E-GEN, and each test with TAU, follow-up will also be conducted at 6, 9, and 12 months. The information collected at months 6 and 9 will be by telephone interviews while participants will return for a physician visit at month 12.

1.4 Design and Outcomes

A multicentre, double-blind, randomized controlled trial examining three different treatment pathways. Participants will be stratified by outpatient treatment site. The primary outcome measure will be change in HAM-D_{17} score between baseline and 8 weeks. Secondary outcomes will be measured by the 16-item Self-Report Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}), 9-item Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7-Item (GAD-7) Scale, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression Efficacy Index (CGI-EI), changes to initial prescribing based on availability of pharmacogenomic data, response rates to psychotropic medication, remission rates, time to response/remission, Udvalg for Kliniske Undersogelser (UKU) side effect rating scale, Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER), weight gain, EuroQol (EQ-5D) and Short Form (36) health survey (SF-36) for quality of life, Pharmacogenetics in Psychiatry Follow-Up Questionnaire (PIP-FQ) for physician's attitude and experience to pharmacogenomic testing, healthcare resource utilization and productivity losses, healthcare costs and cost-effectiveness of GEN, E-GEN and TAU. Evaluation of early and long-term effects on primary and secondary outcomes will be completed.

1.5 Sample Size and Population

This study will enroll 570 participants who present with moderate to severe MDD as measured by a total score of ≥11 on the QIDS-C_{16} and 16-item Self Report Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}), and an inadequate response within the current episode to at least one psychotropic treatment included in the GEN.

2.0 ADMINISTRATIVE INFORMATION

2.1 Title

A three-arm, parallel group, multicentre, double-blind, randomized controlled trial evaluating the impact of GeneSight Psychotropic and Enhanced-GeneSight Psychotropic, on response to psychotropic treatment in outpatients suffering from a major depressive disorder (MDD) and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GeneSight Psychotropic.

2.2 Trial Registration

ClinicalTrials.gov Identifier: NCT02466477

WHO Trial Registration Data Set:

http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02466477

2.3 Protocol Version

Issue date: 2 May 2017 Version: 1.5

2.4 Organizational Structure

2.4.1 MaRS EXCITE

This evaluation is being facilitated through the MaRS Excellence in Clinical Innovation and Technology Evaluation ("EXCITE") program. The EXCITE program connects health technology innovators with experienced, award-winning researchers to get the right evidence and data needed to show the value of the technology and to facilitate discussions with relevant health system stakeholders to determine what it takes to get the technology adopted successfully. The goal of the program is to support the evaluation of new health technologies to develop a robust evidence package that can be used for both regulatory or licensing approval and reimbursement reviews and to connect the innovators with the health system concerning conditions needed for successful adoption of the technology.

2.4.2 Methodology Centre

Methodology Centres are responsible for overseeing the design and execution of EXCITE studies.

Topstone Research is a specialty contract research organization located in Toronto, Ontario Canada selected at the Methodology Centre for this study. Topstone provides supportive research infrastructure for academic institutions and primary care physicians.

The Programs for Assessment of Technology in Health (PATH), based at St. Joseph's Healthcare Hamilton, will be responsible for the economic evaluation associated with the study, as a part of the MaRS EXCITE program.

2.4.3 Trial Monitoring Committee

The Trial Monitoring Committee membership will be comprised of 5 experts (clinicians, scientists, and statisticians) that have relevant expertise and experience in clinical trials, statistics and treatment of MDD but are completely independent of the conduct of the trial, the PIs, the Trial Sponsor and/or the Trial Funders. The PIs may be asked to attend open sessions of the Trial Monitoring Committee meeting.

The Trial Monitoring Committee is the only group involved in the trial that will have access to unblinded data and its role is to review accumulating trial data (focusing on ethical, safety and efficacy endpoints), quality of trial conduct, trial progress, and compliance. It is also responsible for taking into consideration data emerging from other related studies, and in turn making appropriate recommendations. The Trial Monitoring Committee will agree on a Charter of Operations and the frequency of meetings as appropriate.

3.0 BACKGROUND AND RATIONALE

3.1 Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a highly prevalent(1) mental disorder and a leading source of disease burden worldwide(2). Epidemiological studies estimate 12-month and lifetime prevalence of MDD in Canada to be 4% and 10.8% respectively(3). MDD is expected to be the second greatest cause of disability by 2020 and has been shown to cause significant morbidity, affecting people's ability to work, function in relationships, and engage in social activities. Moreover, MDD increases the risk of suicidal ideation, attempted suicide, and death by completed suicide.

Prospective longitudinal studies of patient samples show that MDD is a chronic illness, characterized by remitting and recurrent depressive episodes (4, 5). A major depressive episode is characterized by a low mood or an inability to experience pleasure

(anhedonia), or both, for more than 2 weeks, combined with several cognitive and vegetative symptoms and the occurrence of distress or impairment(6).

Drugs currently available to treat depression can mostly be categorized having their main effect of increasing synaptic levels of the monoaminergic neurotransmitters. These include drugs that elevate norepinephrine (NE) (the tricyclic or tetracyclic antidepressants [TCAs]), those that increase serotonin (5-HT) (the selective serotonin reuptake inhibitors [SSRIs]), and those that increase both NE and 5-HT (the monoamine oxidase inhibitors [MAOIs], and the norepinephrine and serotonin reuptake inhibitors [SNRIs](7, 8). While all antidepressants achieve similar levels of efficacy, treatment failures are relatively high ranging from 30 to 60%(9). Additionally, many of these compounds are associated with significant adverse events (AEs).

3.2 GeneSight Psychotropic (GEN)

The GeneSight Psychotropic (GEN) product is a pharmacogenomic decision support tool that helps clinicians to make informed, evidence-based decisions about proper drug selection. More specifically, patients are tested for clinically important genetic variants of multiple pharmacokinetic and pharmacodynamic genes that affect a patient's ability to metabolize, tolerate or respond to medications.

GEN individualizes psychotherapeutic selection and improves response to psychotropic medications by measuring nucleotide variations in eight genes: CYP1A2, CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2D6; SLC6A4, and HTR2A. Results are analyzed using proprietary algorithms to recommend the selection and dosing of the 33 most commonly prescribed Health Canada approved antidepressant and antipsychotic medications (see Appendix I) including a full representation of the SSRI and SNRI drug classes. Tricyclic antidepressants, an MAOI, and typical and atypical antipsychotics are also represented. The test generates a report for each patient that stratifies antidepressant and antipsychotic medications into one of three "bins": "Green bin" medications – use as directed, "Yellow bin" medications – use with caution, and "Red bin" medications – use with increased caution and more frequent monitoring. Clinicians receive the easy to implement report within three days of sample collection, which is among the fastest responses in the personalized medicine industry.

The clinical utility of GEN has been evaluated in three previous prospective trials. Hall-Flavin et al.(10) reported the results of an open-label pilot study (n = 44) comparing GEN to treatment as usual (TAU) without the benefit of pharmacogenomic testing. The GEN guided arm demonstrated a 30.8% improvement in the 17-item Hamilton Depression Rating Scale (HAM-D_{17}) score by the end of the 8 week treatment period, compared to an 18.2% improvement in the TAU arm ($p = 0.04$). Results of the larger (n = 165) open-label trial(11) mirrored these findings, demonstrating a 46.9% improvement in HAM-D_{17}

score in the GEN arm, compared to a 29.9% improvement in the TAU arm ($p < 0.0001$). The third trial used a randomized, double-blind trial design (n = 51)(12). Due to the small sample size, the trial was underpowered to detect a significant difference in improvement between the two arms (TAU and GEN). However, effect sizes of improvement reflected those seen in previous trials. The GEN group experienced a 30.8% improvement in HAM-D_{17}, compared to 20.7% in TAU. Odds ratios for response were calculated, showing that GEN-guided participants had a 2.14 times greater likelihood of response compared to TAU participants, which was similar to the 4.67 (smaller trial) and 2.06 (larger trial) odds ratios calculated for the other two earlier studies.

The GEN test can also predict those patients with greater healthcare utilizations, disability days, and other events who were prescribed psychotropic medications whose metabolism and brain responses are not optimally matched with the individual's genetic profile(13).

3.3 Enhanced-GeneSight Psychotropic (E-GEN)

The current GEN test lacks predictive genes for a major complication of antipsychotic drug use: antipsychotic-induced weight gain (AIWG).

An enhanced version of the GEN test, E-GEN, was developed by incorporating 6 new genes (represented by 7 SNPs) patented by CAMH and licensed by Assurex that are predictive for AIWG, to those used in the GEN algorithm (Table 1). An increasing risk level associated with AIWG is estimated by an increasing number of risk genotypes that a given patient possesses among the 7 SNPs.

Table 1. Antipsychotic-Induced Weight Gain Markers. MC4R, melanocortin 4 receptor; CNR1, cannabinoid receptor 1; NPY, neuropeptide Y; GCG, glucagon-like peptide 1 gene; HCRTR2, orexin/hypocretin receptor 2; NDUFS1, NADH dehydrogenase (ubiquinone) Fe-S protein 1.

Gene	Polymorphism
MC4R	Rs489693
CNR1	Rs806378
NPY	Rs16147
GCG	Rs13429709
HCRTR2	Rs3134701 Rs4142972
NDUFS1	Rs6435326

3.4 Study Rationale

Previous studies utilizing an open-label design have shown significant improvement in patient outcomes following use of the GEN test(11). However, although effect sizes were

similar to those seen in the open-label studies, a small (n = 51) blinded, randomized controlled trial(12) (RCT) did not detect a statistically significant outcome. Therefore, the first rationale for this trial is to utilize a double-blinded RCT design to replicate previous findings of improvement in clinical outcomes in participants treated with the benefit of GEN testing. Another rationale for this study is to determine the added benefit of using E-GEN testing, as compared to GEN testing, to guide treatment selection based on pharmacogenomic information. Furthermore, this trial also intends to develop an evidence-based case for the value of GEN and E-GEN to Canadian healthcare payers.

It is expected that results from this trial will be used to inform guidelines for the use of pharmacogenomic testing in the treatment of MDD. Results may also be shared with regulatory bodies in Canada and abroad.

3.5 Choice of Comparators

The comparator chosen for this study is treatment as usual (TAU) which provides a "real world" comparison of standard of care with patients who receive GEN or E-GEN test results.

4.0 OBJECTIVES

4.1 Hypothesis

GEN and E-GEN reduces MDD symptoms and is more cost-effective than TAU for patients suffering from MDD and having had – within the current episode – an inadequate response to at least one psychotropic medication included in GEN. Furthermore, E-GEN improves predictions of patients' clinical responses and provides greater clinical utility as compared to GEN.

4.2 Primary Objectives

The first primary objective of this study is to compare the efficacy of GEN to TAU in improving response to psychotropic treatment in outpatients suffering from a major depressive disorder (MDD) and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GEN.

The second primary objective for this study is to validate the utility of the new CAMH markers and demonstrate the superior predictive capabilities and greater clinical utility of E-GEN as compared to GEN.

4.3 Secondary Objectives

To compare the three intervention alternatives (GEN, E-GEN, and TAU) with respect to:

- MDD symptoms;
- Changes to initial prescribing based on availability of pharmacogenomics data;
- Response rates to psychotropic medication;
- Remission rates;
- Time to response/remission;
- Medication side effects, including weight gain;
- Health-related quality of life;
- Physician's attitude and experience to DNA testing;
- Healthcare resource utilization and productivity losses;
- Total estimated healthcare costs associated with the treatment and management of patients;
- Cost-effectiveness of the GEN and E-GEN technology relative to TAU

5.0 TRIAL DESIGN

This study is designed as a three-arm multi-centre, double-blind (participants and raters), randomized controlled trial to compare the clinical and economic outcomes of GEN, E-GEN and TAU for patients suffering from a MDD and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GEN. Participants will be randomized in a 1:1:1 ratio to each of the three treatment arms.

6.0 METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

6.1 Study Setting

This study will be conducted in an outpatient setting. Participants will be recruited from academic and community hospital outpatient clinics, family health teams and primary health care clinics in Ontario.

6.2 Eligibility Criteria

Patients meeting the following criteria will be approached for study enrollment:

6.2.1 Inclusion Criteria

1. 18 years of age or older;
2. Suffer from a Major Depressive Episode meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria;
3. Have had an inadequate response within the current episode to at least one psychotropic treatment (listed in Appendix I). Inadequate response is defined as inadequate efficacy after 6 weeks of a psychotropic treatment or discontinuation of a psychotropic treatment due to adverse events (AEs) or intolerability;
4. Have each a screening and baseline score on the 16-item Clinician Quick Inventory of Depressive Symptomatology (QIDS-C_{16}) and 16-item Self-Report Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}) rating scales ≥ 11;
5. Be able to understand the requirements of the study and provide written informed consent to participate in this study;
6. Agree to abide by the study protocol and its restrictions and be able to complete all aspects of the study, including all visits and tests.

6.2.2 Exclusion Criteria

Any of the following conditions are cause for exclusion from the study:

1. Patients posing a serious suicidal risk and/or in need of immediate hospitalization as judged by the Investigator;
2. Patients with a diagnosis of Bipolar I or II disorder;
3. Patients with a current Axis I diagnosis of:
    - Delirium
    - Dementia
    - Amnestic and/or other cognitive disorder
    - Schizophrenia or other psychotic disorder;
4. Patients having experienced hallucinations, delusions, or any psychotic symptomatology within the current depressive episode or during prior depressive episodes;
5. Patient is currently in an inpatient facility;
6. Patients with a history of hypothyroidism unless taking a stable dose of thyroid medication and asymptomatic or euthyroid for at least 6 months;

7. Patients who meet DSM-IV-TR criteria for any significant current substance use disorder;
8. Patients with:
    - hepatic insufficiency (three times the upper limit of normal (ULN) for aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)); liver transplant recipient; cirrhosis of the liver;
    - malignancy (except basal cell carcinoma) and/or chemotherapy within 1 year prior to screening; malignancy more than 1 year prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications;
    - significant unstable medical condition or life threatening disease with anticipated survival of less than 6 months;
    - need for therapies that may obscure the results of treatment and/or of the study;
9. Participation in another clinical trial within 30 days of the screening visit;
10. Anticipated inability to attend scheduled study visits;
11. Patients who in the judgment of the Investigator may be unreliable or uncooperative with the evaluation procedure outlined in this protocol;
12. Patients with a history of prior pharmacogenomic testing;
13. Any change in psychotropic medication (including change in dosage) between screening and baseline;
14. Patients currently receiving electroconvulsive therapy (ECT), deep brain stimulation (DBS) or transcranial magnetic stimulation (TMS) treatments, or currently scheduled to receive maintenance treatments of ECT, DBS, or TMS during the course of the study;
15. Patients who self-report to be pregnant or lactating;
16. Patients with a history of gastric bypass surgery

7.0 INTERVENTIONS

7.1 Interventions

7.1.1 GeneSight Psychotropic (GEN)

Patients randomized to the GEN group will have buccal swabs of their cheeks taken by the clinician and mailed to the Assurex Health Ltd. (ARx) pharmacogenomics lab in a

secure envelope labeled with a unique identifier to ensure accuracy and validity. Once received, the pharmacogenomic laboratory will analyze the sample and determine the patient's genotypes and corresponding phenotypes for each of the genes tested on the GEN panel. These phenotypes will provide a clear picture of how functional each gene is with respect to drug metabolism (for CYP450 genes) and/or drug response (for neurotransmitter transporter and receptor genes).

After laboratory testing is complete and phenotypes are assigned, GEN technology categorizes the green, yellow, or red status of each drug and which footnote(s) will accompany each drug. This is accomplished by integrating the genetic data with the pharmacology for each medication on the GEN panel (see Appendix I), and incorporating data gleaned from Health Canada-approved labels and published literature.

Within three days of sample receipt at the laboratory, results are returned via the GeneSight clinician portal to the treating clinicians in the form of an interpretive report that categorizes medications into three independent bins titled "Use as Directed", the Green Bin, "Use With Caution", the Yellow Bin, and "Use with Increased Caution And With More Frequent Monitoring", the Red Bin. Medications in the Green Bin are least likely to be affected by genetic polymorphisms identified in the tested individual. Medications in the Yellow Bin are at risk for gene-drug interactions that may necessitate alternative dosing or medication selection. Medications in the Red Bin are at higher risk for a gene-drug interaction that may necessitate alternative dosing or medication selection. Guided by these results, the treating physician may decide to modify a participant's psychotropic medication selection, dose, dose regimen and/or number of medications.

7.1.2 Enhanced GeneSight Psychotropic (E-GEN)

All procedures for patients randomized to the E-GEN arm will be the same as for patients randomized to the GEN arm except that for E-GEN, the pharmacogenomic laboratory will also analyze each patient's genotypes and corresponding phenotypes for the 7 CAMH markers for AIWG. The treating clinicians will receive an interpretive report that reflects all of the E-GEN genes.

Guided by the results from E-GEN, the treating physician may decide to modify a participant's psychotropic medication, in terms of type of medication, dose, dose regimen and/or number of medications.

7.1.3 Treatment as Usual (TAU)

Patients randomized to the TAU arm will also have their DNA collected and a pharmacogenomics-based interpretive report will be generated using GEN testing. However, this report will not be shared with the treating clinicians until up to 28 days prior to the completion at 12 months of the study at which point the report will be provided to

the participant by the treating clinician. Therefore, patients in this arm will receive clinical treatment as usual, without the use or knowledge of genotyping results by their treating clinicians.

7.2 Modifications

At any time point, clinicians can modify a participant's medication based on their clinical judgment. Any switch or change in medications will be recorded on the CRF accordingly.

Women of childbearing age are advised to use a method of birth control during the course of the study. If they intend to get pregnant during the course of the study, then they should advise their primary care physician and/or psychiatrist to ensure that the pharmacotherapy being prescribed can be assessed for safety in pregnancy.

7.3 Concomitant Care

During the study, patients will be allowed to use concomitant medications at the Investigators' discretion. The dose and dose regimen of concomitant medications will be recorded on the CRFs.

8.0 OUTCOMES

8.1 Primary Outcome Measure

8.1.1 17-Item Hamilton Depression Scale (HAM-D_{17})

The primary outcome will be the mean change in the HAM-D_{17} score between baseline and 8 weeks. The HAM-D_{17} assesses mood, feelings of guilt, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms(14-16) (see Appendix II).

8.2 Secondary Outcome Measures

8.2.1 Clinical Outcome Measures of MDD Symptoms and Medication Side Effects

i. 16-Item Self-Report Quick Inventory of Depressive Symptomatology (QIDS-SR16)

The QIDS-SR16 is a patient reported measure designed to assess the severity of depressive symptoms(17, 18). The scale assesses the nine DSM-IV criteria symptom domains for major depression: sad mood, concentration, self-outlook, suicidal ideation, involvement, energy/fatigability, sleep disturbance (4 items: initial, middle, late insomnia, and hypersomnia), appetite/weight increase/decrease (4 items), and psychomotor agitation/retardation (2 items) (see Appendix III).

ii. 9-Item Patient Health Questionnaire (PHQ-9)

The PHQ-9 consists of nine questions, rated 0–3 according to the increased frequency of difficulty experienced in each area covered. Scores are self-rated by patients, with a possible range of 0–27, are summed and can then be interpreted as follows: no depression (0), minimal (1–5), mild (6–9), moderate (10–14), moderately severe (15–19), or severe (>20) depression (see Appendix IV).

iii. Generalized Anxiety Disorder 7-Item (GAD-7) Scale

The GAD-7 is a brief measure of symptoms of anxiety, based on diagnostic criteria described in DSM-IV(19). It consists of seven questions and is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all", "several days", "more than half the days," and "nearly every day," respectively (see Appendix V).

iv. Clinical Global Impression (CGI)

The Clinical Global Impression Scale (CGI) is a brief clinician-rated instrument that consists of three different global measures (see Appendix VI):

- Severity of illness: overall assessment of the current severity of the patient's symptoms (CGI-S);
- Global improvement: overall comparison of the patient's baseline condition with his current state (CGI-I);
- Efficacy index: overall comparison of the patient's baseline condition to a ratio of current therapeutic benefit and severity of side effects (CGI-EI).

v. Changes to initial prescribing based on availability of pharmacogenomic data

The influence of pharmacogenomic data on a physician's initial prescription for both GEN and E-GEN will be evaluated by documenting the psychotropic medication prescribed before the availability of the pharmacogenomics data. This will be compared to changes (if any) to the physician's prescription when pharmacogenomics data becomes available.

vi. Response Rates to Psychotropic Medication

A responder is defined as a participant who satisfies the following criteria:

- HAM-D_{17}: a 50% change from baseline in total scale score;

vii. Remission Rates

A remitter is defined as a participant who satisfies the following criteria:

- HAM-$D_{17} \leq 7$;

viii. Time to response or remission

Time to response or remission of depressive symptoms over 8 weeks and 12 weeks, and maintenance of response/remission up to 12 months as measured by the HAM-D_{17}.

ix. Udvalg for Kliniske Undersogeler (UKU) Side Effect Rating Scale

The UKU side effect rating scale, which is available as a patient self-rated assessment, is a comprehensive scale designed to assess the side effects in patients treated with psychotropic medications (see Appendix VII).

x. Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)

The FIBSER is a reliable and valid self-rated global measure of these three domains of side effects (frequency, intensity, and burden) in a population receiving treatment for depression (see Appendix VIII).

xi. Weight Gain

The side effect of AIWG will be evaluated by measuring study patients' weight and waist-to-hip ratio at baseline and at every visit.

xii. Medication Compliance

Medication compliance or adherence will be evaluated using two validated questionnaires, the Morisky 8-item medication adherence scale and the Brief Adherence Rating Scale (BARS), as well as prescription filling frequency between study visits to evaluate persistence and to validate costs of medication use(20-24).

8.2.2 Clinical Outcome Measures of Health Related Quality of Life

i. EuroQol (EQ-5D-5L)

The EQ-5D is designed for self-completion and assesses health across five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the 5-level versions of EQ-5D (EQ-5D-5L), each domain has five levels of severity; health 'today' is assessed (See Appendix IX). The EQ Visual Analogue scale (EQ VAS) is a single 20 cm vertical visual analogue scale, with a range of 0 to 100, where 0 is the worst and 100 is the best imaginable health.

ii. Short Form (36) Health Survey (SF-36)

The SF-36 is a generic health status profile measure, consisting of eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health(25). These eight dimensions produced separate scores by taking a simple summation of individual item responses, and applying a linear transformation, in order to place them onto a 0 to 100 scale (see Appendix X).

8.2.3 Economic Outcome Measures

i. Healthcare Resource Utilization and Productivity Losses

Resource utilization and productivity losses incurred by GEN, E-GEN and TAU patients will be captured throughout the study. Information to be collected includes: physician visits (general practitioners, psychiatric, and other specialties), hospital utilization (psychiatric and non-psychiatric), emergency department visits (psychiatric and non-psychiatric institutions), medication use (antidepressants, antipsychotics, and other medications), and laboratory tests. For patients employed at the beginning of the study, productivity losses will be captured. This includes absenteeism (the number of days out of work) and number of disability claims (both short and long term) filed.

Participants will complete an economic questionnaire to capture healthcare resource utilization and productivity losses. Since participants may differ in terms of their baseline resource utilization, the questionnaire will be administered at baseline to document historical resource utilization, over the 3 months preceding, the intervention. Appropriate unit costs for Ontario will then be assigned to the data collected in order to provide an indication of the relative costs associated with receiving GEN, E-GEN and TAU.

Data on patient health care resource utilization will also be collected by the Institute for Clinical Evaluative Sciences (ICES). ICES is a research institute in Ontario that is a secure and confidential repository for publicly-funded administrative health data. Data on physician visits, hospitalizations, emergency department visits, and drug costs covered by the Ontario Drug Benefits (ODB) program are available for all Ontario residents and costs are accessible at the individual level through use of an encrypted health card number. Primary data collected from the study will also be linked via health card number, encrypted at ICES, to the ICES administrative databases for patients who had consented to data linkage. As before, costs associated with health services utilization will be based on utilization described above, with standard unit costs for Ontario as a multiplier.

The costs information captured (from economic questionnaire and ICES) will be used to conduct the economic evaluation of introducing GEN and E-GEN as compared to TAU. A trial-based economic evaluation will be conducted by comparing 1-year costs and outcomes associated with the different treatment arms. Since various treatments are compared in this analysis, an efficiency frontier will be created by ranking all options by costs and effectiveness. Any treatments dominated by other treatments having lower costs and higher efficacy will be eliminated from the analyses. In addition, any strategy dominated through the

principle of extended dominance will also be eliminated. Extended dominance rules out any intervention that is dominated by a linear combination of other strategies which produce greater benefit at a lower cost. The remaining options will form the efficiency frontier and incremental cost-effectiveness ratios will be calculated by comparing each option to the next one. Sampling uncertainty will be dealt by bootstrapping costs and effects. The short term results of the trials will be extrapolated to a longer time horizon (e.g. 5 years) by developing a decision analytic model (e.g. Markov model). A probabilistic analysis will be conducted to account for the uncertainty in the model parameters and modeling assumptions will be tested using sensitivity analyses. For both the trial-based and modeling-based economic evaluations, a cost-effectiveness plane will be used to present the results and show the efficiency frontier. Multiple cost-effectiveness acceptability curves will be used for presenting the results of the trial- and model-based economic evaluations.

8.2.4 Other Outcome Measures

i. Pharmacogenetics in Psychiatry Follow-Up Questionnaire (PIP-FQ)

The PIPFQ is a questionnaire (developed by CAMH) to evaluate physicians' attitude and experience to pharmacogenetics testing (see Appendix XI). Information is solicited from the physician on the processing of the physician's last referral, and for the entire study at 12 months.

9.0 STUDY TIME SCHEDULE

Study evaluation measures will be obtained over a 1-year period and will consist of seven scheduled assessments, not including screening and enrollment (Figure 1). Assessment visits will occur at baseline, 4 weeks, 8 weeks, 12 weeks, 6 months, 9 months and 12 months following randomization. The short-term follow-up visits will occur up to and including 12 weeks with the assessment of the primary outcome at 8 weeks, followed by long-term study visits at 6, 9 and 12 months. The following outlines the evaluations to be completed at each of the visits.

Figure 1. Study Time Schedule

Time Point	STUDY PERIOD								Early Termination Visit (ET)
	Screening/ Randomization	Baseline	Short-term visits			Long-term follow-up			
	- t1 (Visit 1)	t0 (Visit 2)	Week 4 (Visit 3)	Week 8 (Visit 4)	Week 12 (Visit 5)	Month 6 (Visit 6)	Month 9 (Visit 7)	Month 12 (Visit 8)	
ENROLLMENT									
Informed consent	x								
Eligibility screening	x								
Randomization	x								
Eligibility baseline		x							
INTERVENTIONS									
GeneSight Psychotropic (GEN)		—	—	—	—	—	—	—	
Enhanced GeneSight Psychotropic (E-GEN)		—	—	—	—	—	—	—	
Treatment as usual (TAU)		—	—	—	—	—	—	—	
ASSESSMENTS									
Buccal swab for genotyping	x								
Vital signs	x								
Mini International Neuropsychiatric Interview (MINI) for Axis 1	x								
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD	x								
DSM-IV-TR criteria for current substance use disorder	x								
Phlebotomy for laboratory panel	x								
Biobank sample	x								
Urine sample for drug screen and laboratory panel	x								
16-item Clinician Quick Inventory of Depressive Symptomatology ($QIDS\text{-}C_{16}$)	x								
16-item Self Report Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$)	x	x	x	x	x			x	x
Changes to initial prescribing based on availability of pharmacogenomic data	x	x							
Medical history and psychiatric history	x	x							
Psychotropic medication history (current and past) and response	x	x							
Past (within one month) concomitant non-psychotropic medications	x	x							
Current concomitant non-psychotropic medications	x	x	x	x	x	x	x	x	x
Demographics, Employment, Insurance		x							
Smoking status and amounts		x	x	x	x			x	x
Height		x							
Weight and waist-to-hip ratio		x	x	x	x			x	x
Adverse events (AEs)		x	x	x	x			x	x
Pharmacogenetics in Psychiatry Follow-Up Questionnaire (PIPFQ)		x							x
17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$)		x	x	x	x	x	x	x	x
9-item Patient Health Questionnaire (PHQ-9)		x	x	x	x			x	x
Generalized Anxiety Disorder 7-Item (GAD-7) Scale		x	x	x	x			x	x
Clinical Global Impression of Severity (CGI-S)		x			x			x	x
Clinical Global Impression of Improvement (CGI-I)					x			x	x
Clinical Global Impression Efficacy Index (CGI-EI)					x			x	x
Udvalg for Kliniske Undersogeler (UKU) side effect rating scale		x	x	x	x			x	x
Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)		x	x	x	x			x	x
EuroQol (EQ-5D-5L)		x			x	x	x	x	x
Short Form (36) Health Survey (SF-36)		x			x	x		x	x
Healthcare resource utilization and productivity losses		x	x	x	x	x	x	x	x
Current psychotropic medication and psychotropic medication trials since last visit		x	x	x	x	x	x	x	x
Medication adjustments (including dose changes, switching, augmentation and discontinuation)		x	x	x	x			x	x
Medication compliance: Morisky 8-item and BARS			x	x	x	x	x	x	x

9.1 Screening Visit (Visit 1)

Following informed consent, all consecutive patients at the recruiting centres will be screened against the inclusion/exclusion criteria outlined previously. A screening log will be maintained at each of the centres.

Potential patients will be provided with a study information sheet describing the purpose and design of the study as well as the nature of the interventions and time commitment. Written informed consent will be obtained prior to performing any study procedures. In addition, the Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and the Research Ethics Board (REB)/Independent Ethics Committee (IEC). It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per applicable regulations.

The following will be performed at the screening visit:

- Administer informed consent;
- Perform buccal swabs for GEN and E-GEN tests;
- Buccal swabs will be obtained and sent to AssureRx laboratory. A buccal swab sample will be analyzed for the pharmacogenomic testing immediately upon receipt at AssureRx. The unanalyzed buccal swabs and associated isolated DNA will be stored at AssureRx laboratory (see Appendix XVI, Part a). The sample will be de-identified, but matched to clinical data with the unique patient identification number.
- Record patient age;
- Review and record medical and psychiatric history;
- Review and record past and current psychotropic medications including response;
- Review and record past (within three months) and current concomitant non-psychotropic medications;
- Obtain vital signs;
    - Vital signs, including temperature, heart rate, sitting systolic and diastolic arterial blood pressure and radial artery pulse rate. Vital signs should be measured with the patient seated and rested at least 5 minutes.
- Perform psychiatric assessments including:
    - Mini International Neuropsychiatric Interview (MINI) for Axis 1
      The MINI was developed as a short and efficient diagnostic interview to be used in clinical as well as research settings(26) (see Appendix XII). It follows DSM-IV and the ICD-10 criteria for psychiatric disorders, screening for 17 Axis I disorders, with brief suicidality and antisocial personality modules. The Axis I disorders included in the MINI were selected based upon the 12-month

prevalence reported in the Epidemiologic Catchment Area Study(27) and the National Comorbidity Survey(28). The MINI has been validated in the U.S. and Europe and administration time ranges from approximately 15-20 minutes for individuals with few positively endorsed symptoms to 20-30 minutes for individuals who meet criteria for current diagnoses.

- DSM-IV-TR criteria for MDD
  The diagnostic criteria for MDD, single or recurrent are shown in Appendix XIII.
- DSM-IV-TR criteria for current substance use disorder
  The diagnostic criteria for current substance use disorder are shown in Appendix XIV.
- 16-Item Clinician Quick Inventory of Depressive Symptomatology (QIDS-C_{16})
  The QIDS-C_{16} has been extensively evaluated in patients with MDD(17, 18).Similar to the QIDS-SR_{16}, the scale assesses the nine DSM-IV criteria symptom domains for major depression: sad mood, concentration, self-outlook, suicidal ideation, involvement, energy/fatigability, sleep disturbance (4 items: initial, middle, late insomnia, and hypersomnia), appetite/weight increase/decrease (4 items), and psychomotor agitation/retardation (2 items) (see Appendix XV).
- QIDS-SR_{16}

- Collect blood for safety laboratories (hematology, and serum biochemistry). Blood samples will be collected for the following clinical laboratory tests:
  - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.
  - Serum chemistry: sodium, chloride, potassium, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, triglycerides, cholesterol, HDL, and LDL.
  - Any abnormal laboratory value must be assessed, with written notation, by the Investigator. If an abnormal laboratory value is clinically significant, the Investigator must immediately contact the medical monitor to discuss the patient's continued eligibility in the trial.
- Collect blood for de-identified DNA and RNA pharmacogenomic research biobank;
  - An additional aliquot of blood will be collected and stored for future pharmacogenomic research at the CAMH laboratories (see Appendix XVI, Part b). The sample will be de-identified, but matched to clinical data with the unique patient identification number.
- Collect urine sample for drug screen;
  - Urine samples will be collected for drug screening (barbiturates, cannabinoids, cocaine, and opiates).

    - Any abnormal blood laboratory value must be assessed, with written notation, by the Investigator. If an abnormal laboratory value is clinically significant, the Investigator must immediately contact the medical monitor to discuss the patient's continued eligibility in the trial.
- Collect information on physician's prescription (including any changes) to patient's psychotropic medication based on information available at this visit;
- Collect information on history of prior pharmacogenomics testing;
- Collect information on current or recent (30 days) enrollment in other studies;
- Evaluate patient against the inclusion/exclusion criteria.

After signing an informed consent form (ICF), the patient has 2 weeks to be evaluated for enrollment in the study. Although the Screening Visit window is 2 weeks prior to enrollment, it is preferable that the participant be assessed at least 3 days prior to enrollment since the genotype results and GeneSight report typically take 2 or 3 days to be issued after receipt of buccal swabs.

The Investigator should contact the medical monitor, as clinically necessary, if the rescheduled visit will extend the screening beyond 2 weeks.

Patients' psychotropic medication should not be modified (in terms of type and dosage) during the screening period (i.e. between the Screening and Baseline visits), except for treatment with benzodiazepines.

Each patient will be assigned a unique patient identifier (UPI). At the Screening Visit, each patient will be assigned a screening number upon signing the ICF. All screening numbers will be assigned by the site in strict numerical sequence and no numbers will be skipped or omitted (e.g., each patient will be assigned to the lowest screening number available). The UPI will be on all case report form (CRF) pages.

If at the end of the screening period the participant is found to be ineligible as per the inclusion/exclusion criteria, then the participant will become a Screen Failure and is exited from the study. The UPI will not be reused. If the participant is eligible at the end of the screening period, then the participant will be enrolled and randomized. If the participant is found to be ineligible as per the inclusion/exclusion criteria at baseline, then the subject will become a Randomization Failure.

9.2 Enrollment and Randomization

Patients who meet all the inclusion/exclusion criteria will be enrolled in the study with a 1:1:1 randomization allocation to one of three groups: GEN, E-GEN, or TAU. Investigators will be then given the results of the GEN test for the participants randomized to GEN, and of the E-GEN test for the participants randomized to E-GEN. Investigators will use the report to support their treatment decision based on this information. However, raters and participants will be blinded.

9.3 Baseline Visit (Visit 2)

Within 14 days of Screening Visit, the baseline assessment visit for the study will be completed.

Prior to any change or adjustment in antidepressant medication, the following will be evaluated and recorded:

- Psychiatric or quality of life evaluations:
    - QIDS-SR$_{16}$
    - HAM-D$_{17}$ (Central rater)
    - CGI-S (Treating clinician)
    - PHQ-9
    - GAD-7
    - EQ-5D-5L
    - SF-36
- Patient demographics;

  Patients' date of birth, age, gender, ethnicity, height (without shoes), annual income, highest education, and health insurance coverage will be recorded.
- Medical and psychiatric history;
- The complete medical history will be conducted with a review of all body systems and the patient's past and concurrent illnesses, drug use (including urine drug test), alcohol use, drug allergies, and family medical history. Particular attention will be paid to past psychiatric history, in particular age at first depressive episode, frequency of relapses, response to previous treatments, and other concomitant psychiatric disorders and their treatment.

- Past and current psychotropic medications including response; The generic name of the psychotropic medication, the doses used, start and end date, as well as response to treatment (efficacy and AEs) will be recorded.
- Past (within three months) and current concomitant non-psychotropic medications (including nicotine replacement and smoking cessation medications); The generic name of the medication, the doses used, start and end date will be recorded.
- Smoking status and amounts
- Weight (without shoes, with clothes) and waist-to-hip ratio
- Changes (if any) to physician's prescription of psychotropic medication based on availability of pharmacogenomics data in GEN and E-GEN
- PIP-FQ
- UKU side effect rating scale
- FIBSER
- AEs
- Medication adjustments (including dose changes, switching, augmentation and discontinuation)
- Health resource utilization and productivity losses

9.4 Week 4 Visit (Visit 3)

Participants will return to the study centre at the end of Week 4 ± 4 days (Visit 3) of the study. The following will be evaluated and recorded:

- Psychiatric or quality of life evaluations:
    - QIDS-SR_{16}
    - HAM-D_{17} (Central rater)
    - PHQ-9
    - GAD-7
    - Morisky scale (med compliance)
    - BARS scale (med compliance)
- Smoking status and amounts
- Weight and waist-to-hip ratio

- Current psychotropic medication and psychotropic medication trials since last visit
- Current concomitant non-psychotropic medications (including nicotine replacement and smoking cessation medications)
- UKU side effect rating scale
- FIBSER
- AEs
- Medication adjustments (including dose changes, switching, augmentation and discontinuation)
- Health resource utilization and productivity losses

9.5 Week 8 Visit (Visit 4)

Participants will return to the study center at the end of Week 8 ± 4 days (Visit 4) of the study. The evaluation at this visit will be the same as that completed at Week 4 (Visit 3).

9.6 Week 12 Visit (Visit 5)

Participants will return to the study center at the end of Week 12 ± 4 days (Visit 5) of the study. In addition to the evaluations conducted at Week 8, the following will also be assessed:

- Psychiatric or quality of life evaluations:
    - CGI-S (Treating clinician)
    - CGI-I (Treating clinician)
    - CGI-EI (Treating clinician)
    - EQ-5D-5L
    - SF-36
    - Morisky scale (med compliance)
    - BARS scale (med compliance)

9.7 Long-Term Follow-Up - Months 6, 9 and 12 Visits (Visits 6, 7 and 8)

The long-term follow-up visits at the end of months 6 and 9 ± 14 days (Visits 6 and 7) will be completed by telephone. The following will be evaluated at these visits:

- Psychiatric or quality of life evaluations:
    - $HAM\text{-}D_{17}$

    - EQ-5D-5L
    - SF-36 (only at month 6)
    - Morisky scale (med compliance)
    - BARS scale (med compliance)
- Current psychotropic medication and psychotropic medication trials since last visit
- Current concomitant non-psychotropic medications (including nicotine replacement and smoking cessation medications)
- Health resource utilization and productivity losses
- Documentation of disclosure of GEN report to participant at month 12 visit
- Participants will return to the study center at the end of month 12 (Visit 8) ± 21 days of the study. The following will be evaluated at this visit:
- Psychiatric or quality of life evaluations:
    - QIDS-SR$_{16}$
    - HAM-D$_{17}$ (Central rater)
    - CGI-S (Treating clinician)
    - CGI-I (Treating clinician)
    - CGI-EI (Treating clinician)
    - PHQ-9
    - GAD-7
    - EQ-5D-5L
    - SF-36
- Smoking status and amounts
- Weight and waist-to-hip ratio
- Current psychotropic medication and psychotropic medication trials since last visit
- Current concomitant non-psychotropic medications (including nicotine replacement and smoking cessation medications)
- UKU side effect rating scale
- FIBSER
- AEs

- Medication adjustments (including dose changes, switching, augmentation and discontinuation)
- Medication compliance
- Health resource utilization and productivity losses

9.8 Early Termination (ET) Visit

If ET occurs, the participant should attend an in-clinic visit as soon as possible to complete ET procedures that will consist of all procedures scheduled for Week 12 (refer to section on Week 12 Visit (Visit 5)).

9.9 Unscheduled Visits

Investigators may see participants for clinical management of their depression at any time. There is no "Unscheduled Visit" in this study but the visit should be recorded in the patient chart as per standard clinical practice.

10.0 SAMPLE SIZE

The study will recruit participants from approximately 8-12 sites stratified into 2 clusters. CAMH will constitute one study site and a single stratified cluster. The remaining sites will constitute the second cluster. The sample size required for this study was calculated using effect size estimates drawn from a previous study conducted by Hall-Flavin et al.(11) Assuming an effect size of 0.30 in HAM-D_{17} score favoring the treatment group, intra class coefficient between clusters of 20%, statistical power of 90%, an alpha level of 0.05, and an expected 16.7% rate of premature discontinuation (based on ongoing studies and experience with the intervention) by Week 8 (primary endpoint), a total of 570 participants (i.e., 190 per treatment arm) are required to detect the same effect in this study. Sample size calculations were determined using SAS (SAS Institute, Inc., Version 9.3, Cary, NC).

11.0 RECRUITMENT

Approximately 8-12 study centres will participate in this study in order to enroll the number of participants outlined above. It is estimated that this study will take approximately 36 months to complete. This timeline is based on a 24-month participant recruitment timeframe and also assuming the collection of 8-week and 1-year follow-up data to examine the consequences of the GEN and E-GEN on patient outcomes, healthcare resource utilization and productivity losses. Changes to these assumptions will require

an adjustment of stated timelines. Participant recruitment plan details can be found in the study Project Management Plan.

12.0 METHODS: ASSIGNMENT OF INTERVENTIONS

12.1 Allocation

12.1.1 Sequence Generation

Participants will be randomly assigned to one of the three treatments arms with a 1:1:1 allocation as per a computer generated randomization schedule stratified by site using permuted blocks of random sizes. The block sizes will not be disclosed, to ensure concealment.

13.0 BLINDING

This study will be conducted under double-blind conditions so that neither the patient nor study staff members involved in patient assessments will know whether the patient is receiving GEN, E-GEN, or TAU. Only the treating clinician at the study site and AssureRx will have knowledge of the intervention arm assigned to the patient.

All assessments will be administered by the site, with the exception of the primary outcome measure (HAM-D_{17}), which will be conducted by 1-2 trained central rater(s) not involved in the clinical care of the individual and blinded to the treatment allocation. The rater will be trained and inter-rater reliability will be determined through rater scoring of the HAM-D_{17} while viewing a DVD-recording of a standardized patient interview.

At randomization, the treating clinician will receive the results of the GEN test for patients allocated to GEN and the results of the E-GEN test for patients allocated to the E-GEN, and may decide to change the participant's treatment based on the results of the test. The treating clinician will therefore not be blinded to treatment allocation. AssureRx will also not be blinded to treatment allocation in order to release the appropriate report (either GEN, E-GEN or no report (TAU)) to the treating clinician and to provide follow-up support to the treating clinician on report interpretation. However, both treating clinician and AssureRx will be blinded to trial data.

14.0 METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

14.1 Data Collection Methods

Data will be collected using a validated electronic data capture (EDC) solution. Electronic case report forms (eCRFs) will be utilized for recording data from each subject meeting the eligibility criteria and being randomized into the study. Electronic access to the CRF will be available to all Investigator sites. All study staff responsible for entering data into the eCRF system will be trained prior to the start-up of the study. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained.

All evaluations performed shall be entered in a timely manner into the eCRF by a member of the site staff delegated responsibility for this specific task by the Principal Investigator of the clinical site. It is the responsibility of the Investigator to ensure that the eCRFs are properly completed. The data in the eCRFs should be consistent with the relevant source documents. The Investigator will sign the designated signature fields of the eCRF to confirm that the information on each screen is accurate and complete. All data must be stored in an unidentifiable form treated with strict confidentiality in accordance with applicable data-protection regulations.

Captured data will be monitored electronically and source data verification (SDV) will take place at the site where all information will be verified against the individual patient records. Any inconsistencies will be presented as queries; either as automatically generated queries if raised by the logical data checks of the eCRF system, or by manually generated queries if raised by the data validation checks or the SDV performed by the data manager (DM) or the CRA respectively. Queries shall be resolved in a timely manner by a trained member of the site staff.

14.1.1 Participant Retention

Once a patient is enrolled, the study site will make every reasonable effort to follow the patient for the entire study period. If a patient fails to return for scheduled visits, a documented effort must be made to determine the reason. If the patient cannot be reached by telephone after two attempts, a certified letter should be sent to the patient requesting contact with the Investigator. This information should be recorded in the study records.

14.1.2 Participant Withdrawal

Early Withdrawal Criteria

Participants will only be withdrawn from the study for the following scenarios:

1. Participant withdraws consent for participation for any reason;
2. Participant is deemed lost to follow-up after all exhaustive measures have been taken to contact and locate the participant or the subject moves away;
3. A protocol violation occurs, whereby the respective Ethics Board or Sponsor requires that a participant is withdrawn from the study;
4. Participant dies;
5. A serious or life-threatening Reportable Event occurred or adverse event that prevents further participation;
6. Investigator judges that for any reason continuation of the study is inappropriate for the patient, this includes non-compliance with study procedures.
7. Participant permanently loses capacity to consent to research during participation in the study.

The reason for early withdrawal from the study will be documented, and all relevant CRFs will be completed. The Sponsor must be notified of all patient withdrawals as soon as possible.

If participant is withdrawn early, all efforts should be made to bring the patient in for an Early Termination (ET) visit as soon as possible (see section on Early Termination (ET) Visit).

If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient and the patient will be removed from the study.

14.1.3 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for any reason at any time and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

15.0 DATA MANAGEMENT

Data Management will be conducted by the sponsor appointed CRO.

Data will be transmitted electronically into the web based EDC system. Data will be coded according to pre-specified dictionaries and in accordance with the CRO Standard Operating Procedures (SOP). The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

A detailed description of the analyses to be performed will be provided in the statistical analysis plan (SAP).

15.1 Inspection of Records

Monitors, auditors, and other authorized representatives of the Sponsor, the REB/IEC approving this study, Health Canada, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study patient's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law. The investigator(s) will be expected to cooperate with such a visit and to provide assistance and documentation (including all study documentation, and patient source data) as requested. Wherever possible de-identified data will be provided to protect participant privacy.

15.2 Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These records include, but are not limited to, the identity of all participating patients, all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence.

The Investigator shall retain study records for a period of 25 years or according to the institutional policy following the date a marketing application is approved for GEN or E-GEN for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved for such indication, for a period of 25 years or according to the institutional policy after all investigations with the test are discontinued and Health Canada is notified.

If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., Sponsor, other investigator) who will accept the responsibility. Notice of this transfer, must be made to the Sponsor.

16.0 STATISTICAL METHODS

16.1 Clinical Analysis

Hall-Flavin et al.(11) experienced significant participant attrition during the course of their investigation. Post hoc analyses using intention-to-treat (ITT) analyses, however, revealed little differences between the observed data and inputed data (e.g., last observation carried forward (LOCF) and estimation/maximization (EM) algorithm imputation). Two analyses will be completed with the study data: under the principle of intention-to-treat all randomized individuals will be analysed, i.e., the Full Analysis Set (FES), and a per protocol (PP) analysis for randomized participants where adherence to the protocol and visits was followed. Therefore, to account for participant attrition in the current study, ITT with multiple imputation with LOCF and EM algorithm imputation will be employed to account for missing data, assuming the data are missing completely at random. To assess the potential impact that the multiple imputation has on the final estimates, an EM algorithm imputation (interative mean imputation) will be used as exploratory sensitivity analysis.

16.1.1 Descriptive Statistics

Continuous variables will be summarized with standard descriptive statistics including means, standard deviations, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. Ninety-five percent confidence intervals will be provided for descriptive statistics, as warranted.

16.1.2 Diagnostics

Prior to formal statistical analyses, diagnostics will be conducted to determine appropriate statistical models. The independence assumption of ANOVA will be tested by examining the correlation between error terms for each dependent variable across levels of the indicator variable. To this end, the Durbin-Watson test statistic will be used to determine if the independence assumption was upheld. Values approaching 2.0 from the left or right were considered to be an indication of independence. The normality assumption will be tested by plotting residuals against the normal probability plot and by deriving the Shapiro-Wilk (S-W) test statistic. The dependent variable will formally be considered to be non-

normally distributed if the p-value for the S-W test was < 0.05. Homogeneity of variance will be tested by employing the statistic derived by Brown and Forsythe. If the associated p-value for the test statistic is < 0.05, then the dependent variable will be assumed to exhibit non-constant variance. If a given dependent variable did not meet the above mentioned assumptions (e.g., clustering due to study site), generalized estimating equations (GEEs) will be employed to account for the lack of independence between outcomes using an autoregressive correlation structure and identity link function.

16.1.3 Continuous Outcomes

If the HAM-D_{17} scores from baseline to end of Week 8 of the study meet the assumptions of ANOVA modeling, repeated-measure (i.e., mixed) ANOVA models will be used to model the outcome scores over time. This model accounts for a between-group and within-individual effect, which allows for the examination of average differences between groups while also accounting for the correlation between participant scores between each measurement. If the HAM-D_{17} scores do not meet standard ANOVA assumptions, GEEs will be used to model repeated measurements of outcome scores over time, as these models are more robust to departures from the standard assumptions and also allow the investigator to specify the correlation structure of the repeated measurements. Mean symptom improvement for all continuous measures (i.e., depression scales) will be calculated using the standard formula ($\frac{y2-y1}{y1}$)*-100, where y1 is the baseline score for each participant for each rating scale and y2 is the 8 week score for each participant for each rating scale.

Two hypotheses related to the primary objectives will be tested, where μ_1 is the mean HAM-D_{17} % symptom improvement in the GEN group, μ_2 is the mean HAM-D_{17} % symptom improvement in the E-GEN group and μ_3 is the mean HAM-D_{17} % symptom improvement in the TAU group.

Primary objective (1):

H_0: $\mu_1 = \mu_2 = \mu_3$

H_a: $\mu_1 = \mu_2 > \mu_3$

Primary objective (2):

H_0: $\mu_1 = \mu_2 = \mu_3$

H_a: $\mu_1 < \mu_2 > \mu_3$

For all continuous measures, a responder will be defined as a participant with 50% change from baseline in total scale score. Remitters at week 8 and at week 12 will be defined as HAM-D_{17} ≤7 in each treatment group. Differential time to response/remission of depressive symptoms over 8 and 12 weeks will be plotted using Kaplan-Meier curves and Cox proportional hazard models will test the null hypothesis of no difference in time to response/remission between groups.

16.1.4 Categorical Outcomes

Categorical outcomes (i.e., remission, response) will be analyzed with 2x2 contingency tables, logistic regression, or loglinear models, where appropriate. Relative risk of response and remission will be determined between each treatment arm (i.e., GEN and E-GEN) using the TAU group as the referent group and the standard formula $\frac{a/(a+b)}{c/(c+d)}$, where *a* is the number of responders/remitters in each GEN or E-GEN group, *b* is the number of non-responders/non-remitters in the GEN or E-GEN group, *c* is the number of responders/remitters in the TAU group, and *d* is the number of non-responders/non-remitters in the TAU group. Standard chi-square tests will be used to determine if the relative risk of response/remission is statistically significant between groups. If expected frequencies are too small for asymptotic assumptions, Fisher's exact tests will be employed to test for differences in categorical outcomes between groups. Ninety-five percent confidence intervals will be calculated and provided for the relative risk of response/remission between groups.

16.1.5 Within-Group and Between-Group Composite Phenotype Analyses

A three-level indicator variable (eg., green, yellow, and red categories) will be created using a proprietary algorithm which combines the phenotypes ascribed to each gene for each participant and drug metabolism information for each of the GeneSight panel drugs. This is done to reduce the dimensionality inherent to such data by generating a single composite phenotype for each participant. The final indicator variable will be labeled 'composite_phenotype,' with the first level scored as 'green,' (e.g., use medication(s) as directed) the second level scored as 'yellow,' (e.g., use medication(s) with caution) and the third level scored as 'red' (e.g., use medication(s) with caution and frequent monitoring). If parametric assumptions are upheld, 1-way independent ANOVA models will employed to test the independent ability of the composite phenotype variable to predict each respective continuous outcome (i.e., percent improvement from baseline for HAMD-17) between study groups. If parametric (i.e., standard) assumptions are not met, GEEs will be employed test the independent ability of the composite phenotype variable to predict each respective continuous outcome. Three tests will be conducted for each

continuous outcome: an overall ANOVA test and two planned contrasts involving the comparison of the first level (i.e., green category) to that of the third (i.e., red category), and the first two levels (i.e., green and yellow categories) of the composite phenotype variable to that of the third level. To account for multiple testing, the Sidak correction will be employed using the formula $1 – (1-\alpha)^{1/n}$ where n is the number of independent tests and α is the nominal level (i.e., 05) of statistical significance

16.1.6 Decision Rule

An overall alpha-level of 0.05 will be used to determine statistical significance and all statistical tests will be two-sided. All data will be analyzed using SAS (SAS Institute, Inc., Version 9.3, Cary, NC).

16.2 Economic Analysis

The economic analysis will include a detailed micro costing evaluation. Using the data collected from the trial and ICES as the foundation, this will be based upon both a 'within trial' analysis, as well as modeling and decision analytic techniques to estimate the long-term cost-effectiveness comparing the use of GEN, E-GEN and TAU. Analyses will be carried out from the perspective of the Canadian healthcare payer, but a societal perspective will also be considered (e.g. productivity costs due to absenteeism and disability).

17.0 METHODS: MONITORING

17.1 Data Monitoring

Monitoring visits will be conducted during the study at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries in the eCRF, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities.

Incorrect or missing entries in the CRFs will be queried and will be corrected appropriately.

All clinical data will undergo quality control checks prior to clinical database lock. Edit checks will then be performed for appropriate databases as a validation routine using SAS ® to check for missing data, data inconsistencies, data ranges, etc. Each eCRF is reviewed and signed by the principal investigator (PI).

17.2 Harms

The GEN and E-GEN is not a drug intervention, and this study is an evaluation of the impact of the results report on a patient's major depression.

Contact information for questions regarding GEN and E-GEN for this study is as follows:

Medical Information
Office Phone: 855-891-9415
Fax: 513-492-7946
Email: MedInfo@assurexhealth.com

17.2.1 Definitions

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Any worsening of a preexisting condition (i.e., any clinically significant adverse change in frequency and/or intensity) which is temporally associated with the use of the investigational product is also an AE.

17.2.2 Evaluating, Recording and Reporting of Adverse Events

At each visit all AEs that are observed, elicited by the Investigator, or reported by the participant, will be recorded in the appropriate section of the AE CRF and evaluated by the Investigator.

Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study drug, action taken, and outcome.

Severity of AEs will be graded by the Investigator using the following criteria as guidelines:

1. Mild: Nuisance, barely noticeable.

2. Moderate: Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.

3. Severe: Symptoms significantly interfere with daily activities or sleep.

The relationship of the AE to the study drug should be specified by the Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with study drug.

2. Unlikely Related: The event has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.

3. Possibly Related: The event follows a reasonable temporal sequence from administration of study drug but which could also be explained by concurrent disease or other factors or medications

4. Probably Related: The event follows a reasonable temporal sequence from administration of study drug, unlikely to be attributed to concurrent disease or other factors or medications. A clinically reasonable response may be observed if the study drug is withdrawn or dose reduced.

5. Definitely Related: The event follows a reasonable temporal sequence from administration of study drug and is definitive pharmacologically; cannot to be attributed to concurrent disease or other factors or medications. A clinically reasonable response should be observed if the study drug is withdrawn or dose reduced.

If discernible at the time of completing an AE CRF, a specific disease or syndrome rather than individual associated signs and symptoms should be recorded on the AE CRF. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE CRF (clinically significant laboratory abnormalities are those that are identified as such by the Investigator and/or those that require intervention).

Investigators should follow the Health Canada process for reporting untoward events of marketed medications by submitting a *Canada Vigilance Adverse Reaction Reporting Form* to MedEffect for a Serious Adverse Event (SAE):

A serious adverse event (SAE) is any untoward medical occurrence that at any dose (including overdose) that meets one or more of the following criteria:

- Is fatal, as a direct outcome of the AE

- Is life threatening
  This serious criterion applies if the participant, in the view of the Investigator, is at substantial risk of dying from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.

- Requires or prolongs inpatient hospitalization
  This serious criterion applies if the reported AE necessitates an inpatient admission (in Canada) or a minimum 24-hour inpatient hospitalization (outside Canada) or, if in the opinion of the Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure, a routinely scheduled treatment or a social admission is not an SAE.

- Results in permanent or significant disability/incapacity
  This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the participant's ability to carry out normal life functions.

- Results in a congenital anomaly/birth defect
  This serious criterion applies if a participant exposed to the investigational product gives birth to a child with congenital anomaly or birth defect.

- Requires intervention to prevent damage/permanent impairment
  This serious criterion applies if the reported AE necessitates a medical or surgical intervention to preclude permanent impairment of a body function, or prevent permanent damage to a body structure. An elective procedure is not an SAE.

Important medical events that do not meet any of the criteria above may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

18.0 AUDITING

Audits and inspections may be carried out by the Sponsor's quality assurance department or designee, Health Canada, or other regulatory authorities to whom information on this study has been submitted. All documents pertinent to the study must be made available for such inspection. Informed consent of patients participating in this study must include the authorization to access these source documents.

19.0 ETHICS AND DISSEMINATION

The study will be conducted in compliance with the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), Health Canada (HC) Food and Drug Regulations, and the International Conference on Harmonization (ICH) Guidelines (E6) for Good Clinical Practice and Personal Health Information Protection Act privacy legislation and all applicable Canadian laws and regulations, as well as any local laws and regulations and all applicable guidelines.

20.0 RESEARCH ETHICS APPROVAL

Investigators will agree that the study will be conducted according to the principles of the ICH E6 Guideline on GCP and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

This trial was designed and organised taking all ethical considerations into account. The protocol and the Informed Consent Form will be approved by the relevant competent authorities (CA) and Research Ethics Boards and possibly other public bodies according to local requirements before commencement.

If a protocol amendment is necessary, this will be prepared and submitted to the central or local REB. If the amendment is considered to be substantial, it will be submitted to the CA, REB and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before approvals are obtained, if required. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial (i.e. non-substantial amendments) do not need to be submitted to CA.

Written Informed Consent

The informed consent process must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each patient prior to screening. All ICFs must be approved for use by the Sponsor and receive approval/favorable opinion from an REB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the Sponsor or designee prior to submission to the governing REB and that it is read, signed and dated by all patients subsequently enrolled in the study as well as those currently enrolled in the study if directed by the REB.

21.0 CONSENT OR ASSENT

Site study coordinators will introduce the trial to potential participants identified as meeting the study criteria. The potential participants will be given written and verbal information about the trial (including potential risks and benefits) and will be able to have an informed discussion with the site study coordinator. They are then encouraged to discuss potential participation with others, as they deem appropriate and given at least 24 hours to consider whether or not to provide informed consent. All participants will be told that they are free to withdraw from the trial at any time, without giving a reason and without any effect on their current or future healthcare.

22.0 CONFIDENTIALITY

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Patient names and other patient-level data will be collected and stored in locked file cabinets in areas with limited access at the study site. All reports, data collection, process and administrative forms will contain a patient unique identifier number in order to maintain patient confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by patient unique identifier number. Study findings stored on a computer will be protected in accordance with local data protection laws.

Monitors, auditors, and other authorized representatives of the Sponsor, the REB/IEC approving this study, Health Canada, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study patient's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the GEN or E-GEN may ultimately be marketed, but the patients' identities will not be disclosed in these documents.

23.0 DECLARATION OF INTERESTS

23.1 Financial Disclosure

Sites will ensure that prior to their participation in the study, the Site Investigators and any sub-investigators complete and return to the Sponsor the Financial Disclosure Statement

form provided by the Sponsor. The Site Investigator and any sub-investigators will promptly notify the site and Sponsor of any required revision to their Financial Disclosure Statement during the term of this Agreement and for 1 year following completion of the study. Upon Sponsor's written request following completion of the study, the Site Investigator and any sub-investigators will provide an updated Financial Disclosure Statement form to the Sponsor.

24.0 DISSEMINATION POLICY

The objectives, the content and the results of the present clinical study as well as all further information must be handled as strictly confidential. All data and results are the exclusive property of Sponsor and CAMH.

After completion of the study or when the study data are adequate (in the Sponsor's and CAMH's reasonable judgment), the Investigator(s) may prepare the data derived from the Study for publication or presentation at a medical-scientific meeting. Such data will be submitted to the Sponsor, CAMH and MaRS EXCITE for review and comment prior to publication. In order to ensure that the Sponsor, CAMH, and MaRS EXCITE will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor, CAMH and MaRS EXCITE for review at least 60 days prior to submission for publication, public dissemination, or review by a publication committee. In the event that Sponsor and CAMH coordinate a multi-centre publication, the participation of the Investigator(s) or other representative of the Investigator(s)s as a named author shall be determined in accordance with Sponsor and CAMH publication policy and International Committee of Medical Journal Editors (ICMJE) standards for authorship.

The Investigator agrees that all reasonable comments made by the Sponsor, CAMH, MaRS EXCITE in relation to a proposed publication by the Investigator will be incorporated by the Investigator into the manuscript.

During the period for review of a proposed publication, the Sponsor and CAMH shall be entitled to delay publication in order to protect proprietary information. No publication of any material related to the study may be published without the prior written consent of the Sponsor and CAMH.

Except as requested by law the Sponsor, CAMH, MaRS EXCITE or the Investigator will not reveal the results of the study to a third party without a mutual agreement about the analysis and interpretation of the data.

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26.0 APPENDICES

APPENDIX I: List of Psychotropic Medications Included in the Canadian version of GeneSight Psychotropic (GEN) and Enhanced GeneSight Psychotropic (E-GEN)

Antidepressants
Amitriptyline
Bupropion
Citalopram
Clomipramine
Desipramine
Desvenlafaxine
Doxepin
Duloxetine
Escitalopram
Fluoxetine
Fluvoxamine
Imipramine
Mirtazapine
Nortriptyline
Paroxetine
Selegiline
Sertraline
Trazodone
Venlafaxine

Antipsychotics
Aripiprazole
Asenapine
Chlorpromazine
Clozapine
Fluphenazine
Haloperidol
Lurasidone
Olanzapine
Paliperidone
Perphenazine
Quetiapine
Risperidone
Thiothixene
Ziprasidone

APPENDIX II: 17-Item Hamilton Depression Rating Scale (HAM-D_{17})

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)
0 Absent
1 These feeling states indicated only on questioning
2 These feeling states spontaneously reported verbally
3 Communicates feeling states nonverbally—i.e., through facial expression, posture, voice, and tendency to weep
4 Patient reports VIRTUALLY ONLY these feeling states in his/her spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**
0 Absent
1 Self-reproach, feels he/she has let people down
2 Ideas of guilt or rumination over past errors or sinful deeds
3 Present illness is a punishment; delusions of guilt
4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**
0 Absent
1 Feels life is not worth living
2 Wishes he/she were dead or any thoughts of possible death to self
3 Suicidal ideas or gestures
4 Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA, EARLY**
0 No difficulty falling asleep
1 Complains of occasional difficulty falling asleep—i.e., more than ½ hour
2 Complains of nightly difficulty falling asleep

5. **INSOMNIA, MIDDLE**
0 No difficulty
1 Patient complains of being restless and disturbed during the night
2 Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. **INSOMNIA, LATE**
0 No difficulty
1 Waking in early hours of the morning but goes back to sleep
2 Unable to fall asleep again if he/she gets out of bed

7. **WORK AND ACTIVITIES**
0 No difficulty

1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work, or hobbies
2 Loss of interest in activity, hobbies, or work—either directly reported by patient, or indirect in listlessness, indecision, and vacillation (feels he/she has to push self to work or activities)
3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores or if patient fails to perform ward chores unassisted

8. **RETARDATION** (Slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
0 Normal speech and thought
1 Slight retardation at interview
2 Obvious retardation at interview
3 Interview difficult
4 Complete stupor

9. **AGITATION**
0 None
1 Fidgetiness
2 Playing with hands, hair, etc.
3 Moving about, can't sit still
4 Hand-wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY PSYCHIC**
0 No difficulty
1 Participantive tension and irritability
2 Worrying about minor matters
3 Apprehensive attitude apparent in face or speech
4 Fears expressed without questioning

11. **ANXIETY (SOMATIC)**
Physiological concomitants of anxiety such as: Gastrointestinal—dry mouth, wind, indigestion, diarrhea, cramps, belching; Cardiovascular—palpitations, headaches; Respiratory—hyperventilation, sighing; Urinary frequency; Sweating
0 Absent
1 Mild
2 Moderate
3 Severe
4 Incapacitating

12. **SOMATIC SYMPTOMS, GASTROINTESTINAL**
0 None

1 Loss of appetite but eating without staff encouragement; heavy feelings in abdomen
2 Difficulty eating without staff urging; requests or requires laxatives or medication for bowels or medication for GI symptoms

13. **SOMATIC SYMPTOMS, GENERAL**

0 None
1 Heaviness in limbs, back, or head; backaches, headache, muscle aches; loss of energy and fatigability
2 Any clear-cut symptom rates 2

14. **GENITAL SYMPTOMS**

Symptoms such as: loss of libido, menstrual disturbances

0 Absent
1 Mild
2 Severe

15. **HYPOCHONDRIASIS**

0 Not present
1 Self-absorption (bodily)
2 Preoccupation with health
3 Frequent complaints, requests for help, etc.
4 Hypochondrial delusions

16. **LOSS OF WEIGHT**

0 No weight loss
1 Probable weight loss associated with present illness
2 Definite (according to patient) weight loss
3 Not assessed

17. **INSIGHT**

0 Acknowledges being depressed and ill
1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 Denies being ill at all

APPENDIX III: 16-Item Self-Report Quick Inventory of Depression Symptomology (QIDS-SR$_{16}$)

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:
   - 0 I never take longer than 30 minutes to fall asleep.
   - 1 I take at least 30 minutes to fall asleep, less than half the time.
   - 2 I take at least 30 minutes to fall asleep, more than half the time.
   - 3 I take more than 60 minutes to fall alseep, more than half the time.
2. Sleep During the Night:
   - 0 I do not wake up at night.
   - 1 I have a restless, light sleep with a few brief awakenings each night.
   - 2 I wake up at least once a night, but I go back to sleep easily.
   - 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.
3. Waking Up Too Early:
   - 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   - 1 More than half the time, I awaken more than 30 minutes before I need to get up.
   - 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   - 3 I awaken at least one hour before I need to, and can't go back to sleep.
4. Sleeping Too Much:
   - 0 I sleep no longer than 7–8 hours/night, without napping during the day.
   - 1 I sleep no longer than 10 hours in a 24-hour period including naps.
   - 2 I sleep no longer than 12 hours in a 24-hour period including naps.
   - 3 I sleep longer than 12 hours in a 24-hour period including naps.

Enter the highest score on any 1 of the 4 sleep items (1–4 above) ____

5. Feeling Sad:
   - 0 I do not feel sad
   - 1 I feel sad less than half the time.
   - 2 I feel sad more than half the time.
   - 3 I feel sad nearly all of the time.
6. Decreased Appetite:
   - 0 There is no change in my usual appetite.
   - 1 I eat somewhat less often or lesser amounts of food than usual.
   - 2 I eat much less than usual and only with personal effort.
   - 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.
7. Increased Appetite:
   - 0 There is no change from my usual appetite.
   - 1 I feel a need to eat more frequently than usual.
   - 2 I regularly eat more often and/or greater amounts of food than usual.
   - 3 I feel driven to overeat both at mealtime and between meals.
8. Decreased Weight (Within the Last Two Weeks):
   - 0 I have not had a change in my weight.
   - 1 I feel as if I've had a slight weight loss.
   - 2 I have lost 2 pounds or more.
   - 3 I have lost 5 pounds or more.
9. Increased Weight (Within the Last Two Weeks):
   - 0 I have not had a change in my weight.
   - 1 I feel as if I've had a slight weight gain.
   - 2 I have gained 2 pounds or more.
   - 3 I have gained 5 pounds or more.

Enter the highest score on any 1 of the 4 appetite/weight change items (6–9 above) ____

10. Concentration/Decision Making:
    - 0 There is no change in my usual capacity to concentrate or make decisions.
    - 1 I occasionally feel indecisive or find that my attention wanders.
    - 2 Most of the time, I struggle to focus my attention or to make decisions.
    - 3 I cannot concentrate well enough to read or cannot make even minor decisions.
11. View of Myself:
    - 0 I see myself as equally worthwhile and deserving as other people.
    - 1 I am more self-blaming than usual.
    - 2 I largely believe that I cause problems for others.
    - 3 I think almost constantly about major and minor defects in myself.
12. Thoughts of Death or Suicide:
    - 0 I do not think of suicide or death.
    - 1 I feel that life is empty or wonder if it's worth living.
    - 2 I think of suicide or death several times a week for several minutes.
    - 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.
13. General Interest:
    - 0 There is no change from usual in how interested I am in other people or activities.
    - 1 I notice that I am less interested in people or activities.
    - 2 I find I have interest in only one or two of my formerly pursued activities.
    - 3 I have virtually no interest in formerly pursued activities.
14. Energy Level:
    - 0 There is no change in my usual level of energy.
    - 1 I get tired more easily than usual.
    - 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
    - 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

Appendix 2. Continued

15. Feeling Slowed Down:
   0 I think, speak, and move at my usual rate of speed.
   1 I find that my thinking is slowed down or my voice sounds dull or flat
   2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
   3 I am often unable to respond to questions without extreme effort.
16. Feeling Restless:
   0 I do not feel restless.
   1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.
   2 I have impulses to move about and am quite restless.
   3 At times, I am unable to stay seated and need to pace around.

Enter the highest score on either of the 2 psychomotor items (15 or 16 above) ____

Total Score:____ (Range 0–27)

APPENDIX IV: 9-Item Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(circle one number on each line)

	Not at all	Several days	More than half the days	Nearly everyday
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

APPENDIX V: Generalized Anxiety Disorder 7-Item (GAD-7) Scale

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

APPENDIX VI: Clinical Global Impression (CGI)

1. SEVERITY OF ILLNESS (CGI-S)

Considering your total clinical experience with this particular population, how ill is the patient at this time?

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients

2. GLOBAL IMPROVEMENT (CGI-I)

Rate total improvement compared to baseline, whether or not, in your judgment, it is due entirely to drug treatment.

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally Improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

3. EFFICACY INDEX (CGI-EI)

Rate this item on the basis of DRUG EFFECT ONLY Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as "Moderate" and side effects are judged "Do not significantly interfere with patient's functioning." Record 06

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Does not significantly interfere with patient's	Significantly interfere with patient's functioning	Outweigh therapeutic effect

		functioning		
MARKED – Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
MODERATE – Decided improvement. Partial remission of symptoms	05	06	07	08
MINIMAL – Slight improvement which doesn't alter status of care of patient	09	10	11	12
UNCHANGED OR WORSE	13	14	15	16

APPENDIX VII: Udvalg for Kliniske Undersogeler (UKU) Side Effect Rating Scale

The UKU Side Effect Rating Scale, Self-rating version
UKU-SERS-Pat - Summary Form
(Nord J Psychiatry 2001;55, Supplement 44:5-10)

PLEASE PRINT LEGIBLY USE BLACK BALL POINT PEN ANSWER ALL QUESTIONS

Patient name (init.) ☐☐☐ Sex M ☐ F ☐ Patient no ☐☐☐☐

Date of assessment Day ☐☐ Mth ☐☐ Year ☐☐ Hour Hour ☐☐ Min ☐☐ Assessment No. ☐☐

CHECK THE APPROPRIATE BOX FOR EACH ITEM. THE FOUR RESPONSE ALTERNATIVES IN THE PATIENT FORM CORRESPOND TO DEGREES OF SEVERITY (0-1-2-3). Information on causal relationship might be obtained by interviewing the patient after completion of the self-rating scale.

Item nr	Symptom	Not ass.	Degree last days/weeks				Causal relationship*		
		9	0	1	2	3	imp	pos	prb
1.	**Psychic Side Effects**								
1.1	Concentration difficulties								
1.2	Asthenia/Lassitude/Increased fatigability								
1.3	Sleepiness/Sedation								
1.4	Failing memory								
1.5	Depression								
1.6	Tension/Inner unrest								
1.7	Increased duration of sleep								
1.8	Reduced duration of sleep								
1.9	Increased dream activity								
1.10	Emotional indifference								
2.	**Neurological Side Effects**								
2.1	Dystonia								
2.2	Rigidity								
2.3	Hypokinesia/Akinesia								
2.4	Hyperkinesia								
2.5	Tremor								
2.6	Akathisia								
2.7	Epileptic seizures								
2.8	Paraesthesias								
2.9	Headache								
3.	**Autonomic Side Effects**								
3.1	Accommodation disturbances								
3.2	Increased salivation								
3.3	Reduced salivation (Dryness of mouth)								
3.4	Nausea/Vomiting								
3.5	Diarrhoea								
3.6	Constipation								
3.7	Micturition disturbances								
3.8	Polyuria/Polydipsia								
3.9	Orthostatic dizziness								
3.10	Palpitations/Tachycardia								
3.11	Increased tendency to sweating								

Item nr	Symptom	Not ass.	Degree last ___ days/weeks				Causal Relationship*		
		9	0	1	2	3	imp	pos	prb
4.	**Other Side Effects**								
4.1	Rash								
4.2	Pruritus								
4.3	Photosensitivity								
4.4	Increased pigmentation								
4.5	Weight gain								
4.6	Weight loss								
4.7a	Menorrhagia								
4.7b	Metrorragia								
4.8	Amenorrhoea								
4.9	Galactorrhoea								
4.10	Gynecomastia								
4.11	Increased sexual desire								
4.12	Diminished sexual desire								
4.13	Erectile dysfunction								
4.14a	Ejaculatory dysfunction								
4.14b	Premature ejaculation								
4.15	Orgasmic dysfunction								
4.16	Dry vagina								

* Optional: imp = improbable, pos = possible, prb = probable

Date:	Day	Mth.	Year	Staff Signature:

APPENDIX VIII: Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)

Patient Name:_____ Date:_____

Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)

Instructions: Select the best response for the following three questions.

---

1. Choose the response that best describes the frequency (how often) of the side effects of the medication you have taken within the past week for your depression. Do not rate side effects if you believe they are due to treatments that you are taking for medical conditions other than depression. Rate the frequency of these side effects for the past week.

No Side effects	Present 10% of the time	Present 25% of the time	Present 50% of the time	Present 75% of the time	Present 90% of the time	Present all of the time
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

---

2. Choose the response that best describes the intensity (how severe) of the side effects that you believe are due to the medication you have taken within the last week for your depression. Rate the intensity of the side effect(s), when they occurred, over the last week.

No Side Effects	Trivial	Mild	Moderate	Marked	Severe	Intolerable
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

---

3. Choose the response that best describes the degree to which antidepressant medication side effects that you have had over the last week have interfered with your day-to-day functions.

No Impairment	Minimal impairment	Mild impairment	Moderate impairment	Marked impairment	Severe impairment	Unable to function
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

APPENDIX IX: EuroQol (EQ-5D-5L)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

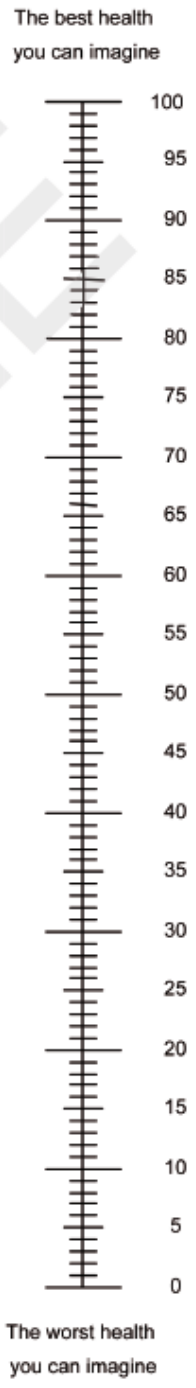
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX X: Short Form (36) Health Survey (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐	☐	☐	☐	☐
b. Have you been very nervous?	☐	☐	☐	☐	☐
c. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d. Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e. Did you have a lot of energy?	☐	☐	☐	☐	☐
f. Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g. Did you feel worn out?	☐	☐	☐	☐	☐
h. Have you been happy?	☐	☐	☐	☐	☐
i. Did you feel tired?	☐	☐	☐	☐	☐

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

11. **How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b. I am as healthy as anybody I know	☐	☐	☐	☐	☐
c. I expect my health to get worse	☐	☐	☐	☐	☐
d. My health is excellent	☐	☐	☐	☐	☐

THANK YOU FOR COMPLETING THESE QUESTIONS!

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APPENDIX XI: Pharmacogenetics in Psychiatry Follow-Up Questionnaire (PIP-FQ)

Pharmacogenetics in Psychiatry Follow-up Questionnaire v2.0
"Genetics of antipsychotic drug metabolism, response and side effects"

Participant ID

Prescription Change Questionnaire: To be completed at baseline & every prescription change

Regarding the GeneSight or Enhanced Genesight provided to you <u>for this participant</u> related to your treatment decision today.

1) Was the information provided to you been easy to *understand* as you made <u>this</u> treatment decision?

Understood Very Well □
Mostly Understood □
Satisfactory Understanding □
Mostly Did Not Understand □
Did Not Understand At All □

2) How *satisfied* were you with the information provided to you for this treatment decision?

Very Satisfied □
Satisfied □
Neutral □
Unsatisfied □
Very Unsatisfied □

3) Was the information given to you, *helpful* in this treatment decisions?

Very Helpful □
Helpful □
Neutral □
Not Helpful □
Very Unhelpful □

Pharmacogenetics in Psychiatry Follow-up Questionnaire v2.0
"Genetics of antipsychotic drug metabolism, response and side effects"

Participant ID

Long-term follow-up questionnaire: To be completed at 12 months or early termination

Regarding the GeneSight or Enhanced Genesight provided to you <u>for this participant</u>

1) Was the information provided to you easy to *understand* since the participant enrolled in the study?

Understood Very Well □
Mostly Understood □
Satisfactory Understanding □
Mostly Did Not Understand □
Did Not Understand At All □

2) How *satisfied* were you with the information provided to you since the participant enrolled in the study

Very Satisfied □
Satisfied □
Neutral □
Unsatisfied □
Very Unsatisfied □

3) Was the information given to you, *helpful* in this treatment decisions since the participant enrolled in the study?

Very Helpful □
Helpful □
Neutral □
Not Helpful □
Very Unhelpful □

If the participant was cared for without the availability of the pharmacogenetic information (treatment as usual), for this participant

1) Would the pharmacogenetic information provided by GeneSight have been *helpful* for treatment decisions since the participant enrolled in the study?

Very Helpful	□
Helpful	□
Neutral	□
Not Helpful	□
Very Unhelpful	□

APPENDIX XII: Mini International Neuropsychiatric Interview (MINI) for Axis 1

Patient Name:			*Patient Number:*			
Date of Birth:			*Time Interview Began:*			
Interviewer's Name:			*Time Interview Ended:*			
ate of Interview:			*Total Time:*			
	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV-TR	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐			
		Past	☐			
		Recurrent	☐			
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	☐
		Past	☐	296.20-296.26 Single	F32.x	☐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	☐
B	SUICIDALITY	Current (Past Month) ☐ Low ☐ Moderate ☐ High	☐			
C	MANIC EPISODE	Current	☐			
		Past	☐			
	HYPOMANIC EPISODE	Current	☐			
		Past	☐	☐ Not Explored		
	BIPOLAR I DISORDER	Current	☐	296.0x-296.6x	F30.x- F31.9	☐
		Past	☐	296.0x-296.6x	F30.x- F31.9	☐
	BIPOLAR II DISORDER	Current	☐	296.89	F31.8	☐
		Past	☐	296.89	F31.8	☐
	BIPOLAR DISORDER NOS	Current	☐	296.80	F31.9	☐
		Past	☐	296.80	F31.9	☐
D	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	☐
		Lifetime	☐			
E	AGORAPHOBIA	Current	☐	300.22	F40.00	☐
	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)				
		Generalized	☐	300.23	F40.1	☐
		Non-Generalized	☐	300.23	F40.1	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	☐
I	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	☐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	☐
J	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
K	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	☐
		Current	☐	297.3/293.81/293.82/	293.89/298.8/298.9	
	MOOD DISORDER WITH	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/	☐
	PSYCHOTIC FEATURES	Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5	
					F31.8/F31.9/F39	☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	☐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		☐ No	☐ Yes ☐ Uncertain		
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	301.7	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

The translation from DSM-IV-TR to ICD-10 coding is not always exact. For more information on this topic see Schulte-Markwort. Crosswalks ICD-10/DSM-IV-TR. Hogrefe & Huber Publishers 2006.

APPENDIX XIII: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD

DIAGNOSTIC CRITERIA FOR 296.2X OR 296.3X
MAJOR DEPRESSIVE DISORDER, SINGLE OR RECURRENT

A. The presence of one or more major depressive episodes.

B. The major depressive episodes are not better accounted for by Schizo-affective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified (NOS).

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode (Note: This exclusion does not apply if any of the manic-like, mixed-like, or hypomanic-like episodes are substance- or treatment-induced or are due to the direct physiological effects of a general medical condition).

Major depressive episode criterion:

A. At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.
   1. Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
   4. Insomnia or hypersomnia nearly every day
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   6. Fatigue or loss of energy nearly every day
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

APPENDIX XIV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for Current Substance Use Disorder

Criteria for Substance Use Disorder:

A pattern of substance use leading to significant impairment or distress, as manifested by one or more of the following:

1. Failure to fulfill major role obligations at work, school, home such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household
2. Frequent use of substances in situation in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. Frequent legal problems (e.g. arrests, disorderly conduct) for substance abuse
4. Continued use despite having persistent or recurrent social or interpersonal problems (e.g., arguments with spouse about consequences of intoxication, physical fights)

APPENDIX XV: 16-Item Clinician Quick Inventory of Depression Symptomology (QIDS-C_{16})

1. Sleep Onset Insomnia
0 Never takes longer than 30 minutes to fall asleep.
1 Takes at least 30 minutes to fall asleep, less than half the time.
2 Takes at least 30 minutes to fall asleep, more than half the time.
3 Takes more than 60 minutes to fall asleep, more than half the time.

2. Mid-Nocturnal Insomnia
0 Does not wake up at night.
1 Restless, light sleep with few awakenings.
2 Wakes up at least once a night, but goes back to sleep easily.
3 Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.

3. Early Morning Insomnia
0 Less than half the time, awakens no more than 30 minutes before necessary.
1 More than half the time, awakens more than 30 minutes before need be.
2 Awakens at least one hour before need be, more than half the time.
3 Awakens at least two hours before need be, more than half the time.

4. Hypersomnia
0 Sleeps no longer than 7-8 hours/night, without naps.
1 Sleeps no longer than 10 hours in a 24 hour period (include naps).
2 Sleeps no longer than 12 hours in a 24 hour period (include naps).
3 Sleeps longer than 12 hours in a 24 hour period (include naps).

Enter the highest score on any 1 of the 4 sleep items (1-4 above) _____

5. Mood (Sad)
0 Does not feel sad.
1 Feels sad less than half the time.
2 Feels sad more than half the time.
3 Feels intensely sad virtually all the time.

6. Appetite (Decreased)
0 No change from usual appetite.
1 Eats somewhat less often and/or lesser amounts than usual.
2 Eats much less than usual and only with personal effort.
3 Eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others.

7. Appetite (Increased)

0 No change from usual appetite.
1 More frequently feels a need to eat than usual.
2 Regularly eats more often and/or greater amounts than usual.
3 Feels driven to overeat at and between meals.

8. Weight (Decrease) Within The Last Two Weeks
0 Has experienced no weight change.
1 Feels as if some slight weight loss occurred.
2 Has lost 2 pounds or more.
3 Has lost 5 pounds or more.

9. Weight (Increase) Within The Last Two Weeks
0 Has experienced no weight change.
1 Feels as if some slight weight gain has occurred.
2 Has gained 2 pounds or more.
3 Has gained 5 pounds or more.

Enter the highest score on any 1 of the 4 appetite/weight change items (6-9 above) _____

10. Concentration/Decision Making
0 No change in usual capacity to concentrate and decide.
1 Occasionally feels indecisive or notes that attention often wanders.
2 Most of the time struggles to focus attention or make decisions.
3 Cannot concentrate well enough to read or cannot make even minor decisions.

11. Outlook (Self)
0 Sees self as equally worthwhile and deserving as others.
1 Is more self-blaming than usual.
2 Largely believes that he/she causes problems for others.
3 Ruminates over major and minor defects in self.

12. Suicidal Ideation
0 Does not think of suicide or death.
1 Feels life is empty or is not worth living.
2 Thinks of suicide/death several times a week for several minutes.
3 Thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide.

13. Involvement
0 No change from usual level of interest in other people and activities.
1 Notices a reduction in former interests/activities.
2 Finds only one or two former interests remain.
3 Has virtually no interest in formerly pursued activities.

14. Energy/Fatiguability
0 No change in usual level of energy.
1 Tires more easily than usual.
2 Makes significant personal effort to initiate or maintain usual daily activities.
3 Unable to carry out most of usual daily activities due to lack of energy.

15. Psychomotor Slowing
0 Normal speed of thinking, gesturing, and speaking.
1 Patient notes slowed thinking, and voice modulation is reduced.
2 Takes several seconds to respond to most questions; reports slowed thinking.
3 Is largely unresponsive to most questions without strong encouragement.

16. Psychomotor Agitation
0 No increased speed or disorganization in thinking or gesturing.
1 Fidgets, wrings hands and shifts positions often.
2 Describes impulse to move about and displays motor restlessness.
3 Unable to stay seated. Paces about with or without permission.

Enter the highest score on either of the 2 psychomotor items (15 or 16 above) _____

TOTAL SCORE: _____ (RANGE 0-27)

APPENDIX XVI: Biological Specimens

a) Unanalyzed Buccal Swabs and Associated Isolated DNA

The unanalyzed buccal swabs and associated isolated DNA will be stored at Assurex Health Ltd., 250 College Street, R-38, Toronto, ON. The test results (the GeneSight report) will be retained indefinitely. The buccal swabs will be stored for three years after the completion of the study.

If a request is made to destroy the samples on an individual basis, they will be destroyed by incineration.

The laboratory director of Assurex Health Ltd. will have access to the unanalyzed buccal swabs and associated isolated DNA. These samples will not be shared with other outside organizations or laboratories, and will not be used for research purposes beyond internal GeneSight assay development or improvement. There will also be no cross-border transfer of these samples.

b) Blood for DNA and RNA Extraction

Blood Collection and Transport

Blood will be collected into tubes containing appropriate anticoagulants so that DNA and RNA can be isolated respectively.

The blood-containing tubes will be transported to the Neurogenetics Lab at CAMH located at 250 College Street, R-50, Toronto, ON. The transport of these tubes will be contracted to a commercial lab services (e.g. LifeLabs Medical Laboratory Services) and will be carried out according to Transportation of Dangerous Goods requirement (http://www.tc.gc.ca/eng/tdg/moc-infectious-type1b-471.html).

Processing Methods

Upon arrival, the DNA and RNA will be isolated and frozen down (at -80°C or in liquid nitrogen) for long term storage and future testing.

All samples will be logged in and bar coded with a unique storage ID.

The samples will retained for 25 years at the Neurogenetics Lab at CAMH located at 250 College Street, R-50, Toronto, ON. Samples will be destroyed at the end of 25 years by incineration. If a request is made to destroy the samples on an individual basis, they will also be destroyed by incineration.

The scientists who will carry out analyses on these materials will not have access to personal identifiers and will not be able to link the results of these tests to personal

identifier information. No individual results will be presented in publications, reports or presentations.

Participants will not be informed on an individual basis of any results from these studies.

The authorized study personnel of the Neurogenetics Lab at CAMH will have access to the DNA and RNA biobank samples. The DNA and RNA samples collected in this study will be used for future research studies at CAMH. CAMH may collaborate with other research organizations, including commercial companies who may want to use the samples and already collected medical information for studying genetic material and substances related to research on psychiatric disorders. Any study data that is sent outside of the hospital will have a number code and will not contain any identifying information about the study participant. There will be no cross-border transfer of these samples.