Study Title:	**Clinical implementation of preemptive pharmacogenomics-guided prescription in psychiatry**
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Co-Principal Investigator (site): *If the study is a collaborative work, please add a site PI (please list all if more sites are involved) from the collaborative institute. Otherwise, please type N/A.*	**Dr Wadha Al-Muftah** Senior director Qatar Genome, Qatar Precision Health Institute, Qatar Foundation

Contents

1. Synopsis

Globally, mental illness poses a huge healthcare challenge, affecting millions of people clinically and economically. A variety of responses and outcomes are observed with the use of different psychotropic medications, with different rates of overall remission from schizophrenia, depression, or bipolar disorder. Drug response can be enhanced through effective dosing and the mitigation of adverse drug reactions by incorporating pharmacogenetic testing into clinical workflows. The Food and Drug Administration (FDA), Clinical Pharmacogenetics Implementation Consortium (CPIC), and Dutch Pharmacogenomic Working Group (DPWG) have issued several drug-gene pairs, including CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4 and HLA-A/HLA-B gene variants, which may influence and predict drug responses. Genetic data with established analytical and clinical validity can be utilized to improve the trial-and-error approach in psychiatry so that patients are prescribed the appropriate drugs at the right dosage. Qatar Genome Program (QGP)/ Qatar Precision Health Institute (QPHI) has an initiative that aims to utilize and implement pharmacogenetic data which may enhance patient clinical outcomes suffering from mental illness, based on clinical guidelines and validated genetic data. It is the ultimate objective of the project that psychiatrists use pharmacogenetic information to accurately predict the effects of psychotropic medications on their patients in order to mitigate the "trial-and-error" procedures during diagnosis and treatment.

2. Abbreviations and Acronyms

CPIC: Clinical Pharmacogenetics Implementation Consortium

DPWG : Dutch Pharmacogenomic Working Group

MDD: Major depressive disorder

3. Introduction/Background

According to the World Health Organization, 1 in 8 people in the world live with a mental disorder (1). Mental disorders are associated with high mortality rates (2). Among the most common mental disorders , Major depressive disorder (MDD)

is often associated with disability and huge impact on the economy(1). Another serious mental condition, schizophrenia, affects 0.6 to 1.9% of the population. Antipsychotics, the standard prescribed treatment for schizophrenics, have an efficacy rate of 60-70% (2).

Many psychotropic medications are currently used to treat mental disorders, primarily through trial and error based on clinical experience and preferences (3). Despite the availability of different treatment options, many patients do not exhibit satisfactory responses and are unable to have remission after taking the medication.

It was found that approximately half of MDD patients did not respond well to their first medication, while only a third of patients went into remission during the first treatment level (4, 5). Furthermore, patients with significant medical, social, and economic burdens receiving antidepressant/antipsychotic treatment also exhibit low adherence rates (3). In accordance, the results of large-scale clinical trials revealed a 75% discontinuation rate of antipsychotic medication due to side effects and tolerability (6, 7).

It was reported that 42% of the variability in antidepressant response has been attributed to genetic polymorphisms (8). There is also evidence that drug-gene pairs can help predict the debilitating side effects of typical and atypical antipsychotics, such as aripiprazole, clozapine, risperidone, thioridazine, and olanzapine (9)

In order to apply personalized approach for psychotropic treatment, biomarkers of different genetic polymorphism can be used. American Psychiatric Association (APA) guidelines for treating MDD acknowledge the impact of interindividual variability affecting safety and efficacy of psychotropic medications(10). Additionally, FDA Guidelines highlighted the value of usage of pharmacogenetic (PGx) test result to reduce adverse drug events and personalize prescribing medications (11). Several studies have been reported that polymorphisms in CYP2D6 and CYP2C19 genes may be useful clinical indicators for prescribing medications for MDD patients. Most psychiatric medications are metabolized by CYP2D6 and CYP2C19 enzymes, which may be altered by functional variants in these genes (12).

The Pharmacogenomics Knowledge Base (PharmGKB) supports evidence on drug-gene pairs involved in psychotropic side effects and treatment response. The PharmGKB assigns clinical annotations based on the level of evidence, where 1A is the highest level. Accordingly, guidelines on genotype-guided antidepressants/antipsychotic prescriptions are issued and they include recommendations for the selection of appropriate dosing and/or medications used to treat psychiatric disorders such as MDD and schizophrenia (13, 14). Nevertheless, there are limitations regarding the clinical utility of highly evident gene-drug pairs that hinder the clinical implementation of genetic-guided prescription of psychiatric medication (15).

Several clinical trials have been conducted to assess the effectiveness of PGx testing in psychiatric care. However, these findings have not yet translated into widespread clinical adoption. The Precision Medicine in Mental Health Care (PRIME Care) Trial is recognized as the first, large-scale international study focusing on the clinical utility of PGx-guided treatment in patients with mental health disorders. This randomized clinical trial evaluated the clinical outcomes associated with PGx testing, comparing PGx-guided treatment with standard care and showed that PGx testing can aid in selecting antidepressants with fewer gene-drug interactions, potentially leading to improved short-term remission rates in patients with MDD (16). Data from over 1,000 adults with MDD who underwent PGx testing using the GeneSight Psychotropic test revealed that combinatorial pharmacogenomic testing could effectively in improving treatment response, decreasing side effects, and enhancing patient satisfaction with care (17, 18). Furthermore, other randomized controlled trials, such as the GUIDED trial (19), have demonstrated that PGx-guided therapy can improve response and remission rates in patients with MDD. Recently, a multicenter, large-scale, prospective study of PREemptive Pharmacogenomic testing for preventing Adverse drug Reactions (PREPARE) study as well demonstrated that PGx-guided treatment can have a beneficial effect in treating the disease in psychiatric patients by reducing the incidence of adverse drug reactions, with only 28% of patients receiving PGx-guided medication management experiencing at least one adverse drug reaction compared to 53% in the control group accompanied with a reciprocal reduction of treatment costs (20).

Despite growing evidence, the adoption of PGx testing into routine mental health care is inconsistently applied due to logistical, educational, and regulatory barriers (21, 22). Furthermore, most implementation efforts have been concentrated

in North America and Europe, with limited evidence from the Middle East or Gulf region. To our knowledge, no comprehensive implementation model currently exists in Qatar or neighboring countries targeting psychiatric disorders through PGx. Our proposal is therefore novel in aiming to develop an integrated PGx implementation framework that encompasses local clinical pathways and prescriber support specific decision to psychiatric pharmacotherapy.

Herein, this study was designed to investigate the clinical utility of PGx testing using a gene panel array of PharmacoFocus platform. The current study aims to analyze the efficacy of pharmacogenetic testing in the selection of drug treatments for psychiatric patients conducted under real-world clinical practice conditions. Furthermore, this study aims to address the implementation gap between evidence and clinical practice by evaluating clinical utility, feasibility, and health system integration of PGx testing within psychiatric care in Qatar which remains underrepresented in global pharmacogenomic research.

4. Objectives

Aims

The study aims to implement the use of PGx information to guide the prescription of psychiatric medications in the clinical setting in Qatar

- The primary objective

To determine whether genotyping-guided prescription and PGx testing can enhance patient outcome and drug tolerance for psychiatric patients who are prescribed antidepressant/antipsychotics within 4-12 weeks.

- The secondary objective

To investigate the frequency of actionable phenotypes, the frequency of incident prescriptions with a combination of a drug with a known gene-drug interaction and the associated actionable genotype, and the effects of gene-drug interactions on pharmacotherapy

5. Indicate if this is a retrospective data review

- ☐ **Retrospective Chart/data Review**
  Please tick the box if your study is retrospective data review or has any retrospective study element (e.g. prospective and retrospective proposals – mixed design)
  Retrospective means the data is already in existence when the project is submitted to the MRC for review

- **Provide the date range of the chart review**
  Please note that the start and end dates for the date range should be prior to study submission date on ABHATH. Dates should be stated in the following format mm/dd/yyyy to mm/dd/yyyy

6. Study Methodology

6.1. Designing and setting

This is a prospective cohort study, to evaluate the effectiveness and clinical utility of the PGx testing in enhancing medication safety and tolerability in 150 Arab patients diagnosed with MDD and schizophrenia recruited during their clinic visit (in clinical setting of inpatients, outpatients or community) to HMC Psychiatry Hospital. Eligible participants will provide 2 ml saliva sample during their clinical visit for DNA extraction and genotyping using a genotyping array in the QBB facility where QGP will be responsible for genotyping, data analysis, validation of procedure and data profiling.

Patients will receive their treatment as part of the routine medical care and will be followed up for 2-4 weeks for early response. Patients who fail to achieve early response to the initial treatment plan based on clinical judgment and / or based on a clinical rating scale are considered for PGx-guided prescription.

Meanwhile, Genetic data will be provided and interpreted. Clinical recommendations will be issued based on current evidence of international guidelines. The recommendations will be conveyed to the clinical pharmacists to evaluate these recommendations in the context of the the patient's current medication (to evaluate drug-drug interaction and drug-drug-gene interaction), medical, and laboratory data.

Following assessment, personalized PGx report with genetic test result will be incorporated in the patient's electronic health record. The clinical recommendations will be also shared with the treating physician for consideration. After the initial follow-up period, a patient who showed poor response or intolerance during the initial follow-up period (4 weeks) is going to be prescribed a new therapy based on their PGx recommendation.

Patients who will receive PGx-guided prescription will be followed up for 12 weeks (2 nd follow-up) and assessed for early response at weeks 2and 4 and remission at weeks 8 and 12. Clinical information and treatment data that are required for the purpose of the research will be collected during the study and during the follow-up period.

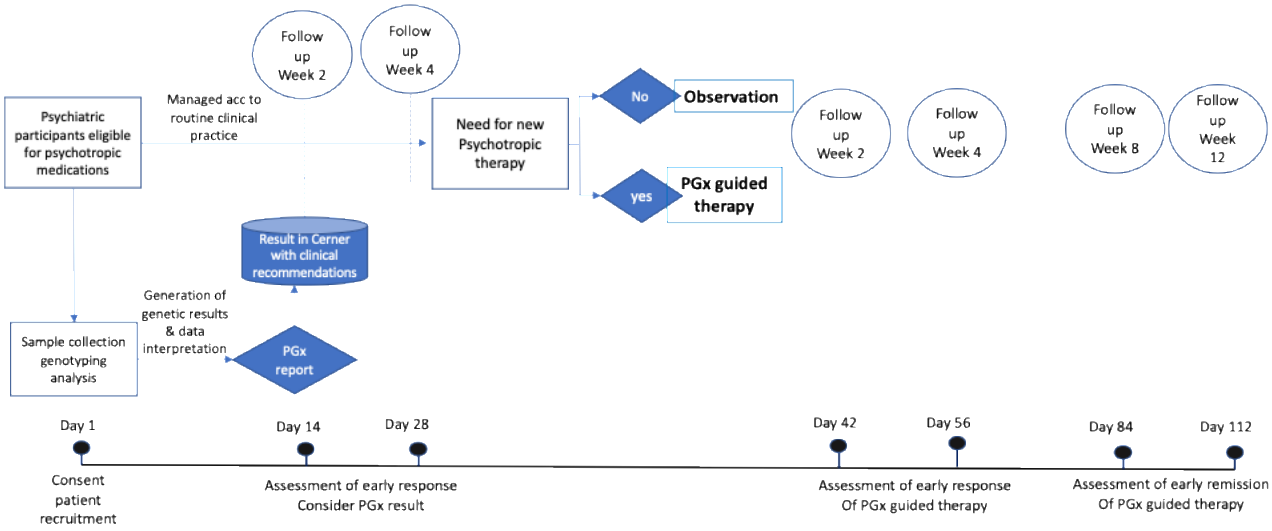

Figure (1): Study Design and workflow

In this regard, the study groups involved in the above workflow (to be managed separately), are either:

A- Naïve psychotropic-treated patient group

Patients with no prior exposure to psychotropic medications (either antipsychotics or antidepressants) before the initiation of the study or trial. These patients are typically treatment-naïve and have not been treated pharmacologically for their psychiatric conditions.

B- Poorly managed psychotropic-treated patient group:

Patients currently on psychotropic medications who exhibit inadequate symptom control, significant side effects, or non-adherence to their treatment regimen, resulting in suboptimal clinical outcomes.

Both naïve and poorly managed groups will be applied separately for each psychiatric disorder under consideration; mainly MDD-targeted with antidepressants, or other psychiatric disorders (ex: bipolar disorder, and schizophrenia) targeted by antipsychotics separately. This approach ensures that the clinical context, treatment history, and management challenges specific to each condition are appropriately addressed.

Criteria	Naïve Group	Poorly managed group
Treatment history	No prior exposure to psychotropics	Current treatment with suboptimal outcomes
Duration of the current therapy	Not applicable	≥6 weeks at therapeutic doses
Symptom management	First-line therapy initiation	Inadequate symptom control
Adverse drug reaction	None (naïve to medications)	Significant ADRs

6.2. GENOTYPING STRATEGY AND CLINICAL DATA COLLECTION

After signing the consent form, the eligible participant will be invited to donate 2 ml saliva sample. DNA extraction will be performed, and genotyping analysis will be operated using a PharmacoFocus array that covers 20000 markers. Genetic variations in gene-associated antidepressants/antipsychotics including CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 are reported. Actionable phenotypes were defined as a genetically predicted poor, intermediate, rapid or ultra-rapid metabolizer phenotype. The Clinical recommendations will be provided in accordance with the clinical guideline CPIC and DWPG with a consideration of evidence level (13, 14, 23)

Clinical and demographic data will be collected from all consented eligible patients.

Table (1): Classes and class rating assessment for gene-drug pairs of antidepressants and antipsychotics medications

Medications	gene	Strength of recommendation	CPIC class	DPWG class	PharmGKB class	FDA label
Amitriptyline	CYP2D6/ CYP2C19	Strong	A	3A/3C	1A	Actionable
Nortriptyline	CYP2D6	strong	A	3C	1A	Actionable
Desipramine	CYP2D6	Strong/optional	B	N.A.	1A	Actionable
Doxepin	CYP2D6/ CYP2C19	Strong/optional	B	3A	1A	Actionable
Imipramine	CYP2D6/ CYP2C19	Strong/optional	B	4A	1A	Actionable

Trimipramine	CYP2D6/ CYP2C19	Strong/optional	B	N.A.	1A	Actionable
Clomipramine	CYP2D6/ CYP2C19	Strong/optional	B	3A/3C	1A	Actionable
Sertraline	CYP2C19	Strong/optional	B	4A	1A	N.A.
Fluvoxamine	CYP2D6	Strong/Moderate	B	N.A.	1A	Actionable
Paroxetine	CYP2D6	Strong	A	4A/4C	1A	Informative
Escitalopram	CYP2C19	Strong/Moderate	A	4C	1A	Actionable
Venlafaxine	CYP2D6	N.A.	A/B	4A	2A	Actionable
Aripiprazole	**CYP2D6/CYP3A4**	Recommended	**B**	**3A**	**3**	**Actionable**
Pimozide	CYP2D6/CYP3A4 /CYP1A2	Recommended	A/B	3A	3	Resting required
Risperidone	CYP2D6/CYP1A2 /CYP3A4/CYP2C19	Recommended	B	4C	1B	informative
Zuclopenthixol	CYP2D6	Recommended	B/C	4A	3	N.A.
Haloperidol	CYP2D6/CYP3A4 CYP1A2	Recommended	B/C	A/C	3	N.A.
Clozapine	CYP2D6, *CYP1A2*	Strong	A	1A	1A	informative
olanzapine	*CYP1A2*	Strong	A	1A	1A	Informative
Vortioxetine	CYP2D6	Strong	NA	A	1A	Informative
Bupropion	CYP2D6	Strong	NA	1A	1A	informative
Duloxetine	CYP2D6	Strong	1A	1A	1A	Informative
Quetiapine	*CYP3A4, CYP3A5*	Strong	NA	1A	1A	informative
Carbamazepine	*HLA-A*31:01, HLA-A*15:02, HLA-B*15:11*	Strong	1A	1A	1A	Testing required

Lithium will be considered in research base with no associated clinical recommendation

6.3. STUDY ENDPOINT AND MEASURED OUTCOME

Patients who received PGx-guided prescription in the second phase of treatment are followed up to assess their early response at the end of week 2-4 and the remission rate at week 8-12.

Clinical effectiveness of antidepressant/antipsychotic pharmacotherapy will be assessed as follows

6.3.1. Scoring system

Assessment timeline

The clinical response is to be assessed in 4 point of time:

1. At the baseline of recruitment
2. To assess the response of the standard therapy in early phase of 2-4 weeks of therapy initiation
3. To assess the response of PGx guided approach in two phases (early-response phase of 2-4 weeks) and early remission phase of 8-12 weeks

The Adverse drug reactions (ADR) is to be assessed in 4 points of time:

1. At the baseline of recruitment specifically for patient with poor response
2. To assess the response of the standard therapy in early phase of 2-4 weeks of therapy initiation
3. To assess the response of PGx guided approach in two phases (early-response phase of 2-4 weeks) and early remission phase of 8-12 weeks

A. Clinical Assessment Tools:

1. Montgomery-Asberg Depression Rating Scale (MADRS):

MADRS is a tool used to assess the severity of symptoms of depression. The tool assess various items include anxiety, irritability, sleep pattern, lack of energy, etc… and a total score is provided to assess the severity level ranged from Normal to severe depression

Tool link: https://www.mdcalc.com/calc/4058/montgomery-asberg-depression-rating-scale-madrs

2. Brief Psychiatric Rating Scale (BPRS): To evaluate psychiatric symptoms (e.g., schizophrenia, psychosis).

BPRS is a tool used to evaluate and assess the severity of symptoms in psychiatric patients. Items of assessment included evaluation of suspiciousness, disorientation, hallucination, disorganization, etc.. The tool can be accessed at https://qxmd.com/calculate/calculator_551/brief-psychiatric-rating-scale-bprs. The interpretation score is provided to assess the severity levels in different domains

B. Assessment tool for ADR:

Glasgow Antipsychotic Side-Effect Scale (GASS): GASS Contain 21 questions to assess the **side effects of antipsychotic medications. It** covers a broad range of side effects associated with antipsychotic use, including extrapyramidal symptoms, metabolic dysfunction, sedation and other neurological disorders. The score is ranged between 0-63 for mild to severe side effects. See attached supplement (1)

2. Antidepressant Side-Effect Checklist (ASEC): To assess side effects of antidepressant medications.

ASEC is a tool used to assess the ADR of antidepressant medications, it is a21 question covers the checklist typically includes items grouped into symptom domains reflecting common antidepressant side effects: Gastrointestinal Symptoms, Central Nervous System Symptoms, Sleep-Related Symptoms, Sexual Dysfunction, Weight and Appetite Changes, Emotional and Behavioral Symptoms and Other Side Effects:

See attached supplement (2)

6.3.2. The primary outcome measures

1- Treatment discontinuation or continuation, The reasons are assessed according to clinical judgments related to efficacy and ADR
2- Assess the time from the therapy initiation till the first assessed early response between 2-4 weeks for PGx-guided regimen.
3- Assess the time from the therapy initiation of Pgx guided prescription till the complete remission between 8-12 weeks first assessed early response between 2-4 weeks for PGx-guided regimen
4- Assess the hospital admission period. Starting from admission till discharge for inpatient wards

6.3 Sample size calculation

- The sample size was calculated for different study arms as follows: A- First Arm is for poorly response participant: the sample size calculation depends on the anticipated mean response and the minimum detectable improvement (effect size)(24) due to the PGx intervention to detect a sustained response of around 35% in the PGx-guided group and expected initial response in the study cohort of 25% (10) with alpha = 0.05 and power = 80%, resulting in a target N of 30 per study group when assuming that allele frequency of assessed pharmacogenes required PGx-guide prescription is 52% and a 20% loss to follow-up. B.- Second arm Second Arm is for newly diagnosed patients receiving PGx intervention: here we will apply pre-post test design (paired t-test) to compare results before and after applying PGx testing, the effect size is 10 with alpha = 0.05 and power = 80%, resulting in a target N of 80 per study group when assuming that allele frequency of assessed pharmacogenes required PGx-guide prescription is 52% and a 20% loss to follow-up. C.Third Third Arm is for newly diagnosed who doesn't apply PGx recommendation: an observational test group studying the effect of medications regardless of PGx results, we assume the study focuses on detecting a significant medication effect in a single group absolute improvement in response score/ minimum detected difference Δ =10 and SD=10 with alpha = 0.05 and power = 80%, resulting in a target N of 25 per study group when assuming that allele frequency of assessed pharmacogenes required PGx-guide prescription is 52% and a 20% loss to follow-up so total number recruited will be 150 participants

7. Study Population and Study Setting/ Location

Hamad Medical Corporation (HMC) Mental health service (MHS) will be the clinical setting of the study. Psychiatric patients with a diagnosis of MDD or schizophrenia and considered for psychotropic medications will be recruited from psychiatry hospital for 2 years. Patients who meet the following inclusion criteria are invited to be part of the study. Participants deemed non-eligible according to their treating physician are going to excluded from the study. Adult eligible participants will be invited to donate biological samples to be genetically analyzed by QPHI to provide genetically guided antipsychotics medication prescription

Inclusion criteria

1- Adult of age 18-65
2- Arab origin: This study focuses on identifying genetic variants and their clinical implications specific to the Arab population. Inclusion of only Arab participants minimizes genetic heterogeneity, ensuring valid, population-specific findings that can directly inform precision medicine initiatives for this community.
   We identify Arab population based on their nationality following QBB protocol (25)
3- Those who are diagnosed with MDD or Schizophrenia (new and previously diagnosis) or other related psychotic or mood disorders based on clinical Judgment
4- Those who are eligible for prescription of psychotropic medications.
5- Provide a written consent for participation

Exclusion criteria

1- Those who have a current diagnosis of delirium, dementia, amnestic or other cognitive disorder, eating disorder,
2- Those who have participated in a clinical trial within the past month
3- High suicide risk
4- Other acute serious psychiatric disorder other than depression and schizophrenia
5- Excessive consumption of alcohol and/or drugs
6- Severe acute or severe chronic somatic diseases
7- Pregnant or lactating women
8- Patients with a severe cognitive impairment, which affects adherence to therapy or the ability to sign the consent, are going to be excluded from the study.
9- Patients with active cancers
10- Having renal failure or severe renal dysfunction identified by Glomerular filtration rate of less than 30 ml/min/1.73 m2
11- Having severe hepatic dysfunction defined by raised serum aminotransferase (x 3 folds of normal levels) and hospitalized for hepatic disease
12- Patients with cardiac dysfunction defined by reduced left ventricular ejection fraction (LVEF less than 35) or significant QTc-interval prolongation more than 500

Participants will be followed by their treating physicians during and after receiving their psychotropic therapy as part of the routine medical care and specified treatment plan. Participants who are recorded to have intolerance/ineffective therapy will be provided a PGx-guided therapy

Clinical information and treatment data that are required for the purpose of the research will be collected during the study and during the follow up period.

8. Study procedures

Please provide an outline and describe in detail the processes and operations of the study, including logistics

8.1 Study Duration and Timelines

(36 MONTH)

Activity	Duration	Timeline	Notes
a. Patient Selection and Recruitment	24 months	Months 1–24	Apply inclusion/exclusion criteria; track and follow up recruitment progress.
b. Informed Consent and Withdrawal Monitoring	36 months	Months 1–36	Continuous process throughout study; ensure proper documentation.
c. Baseline Assessment of Clinical and Laboratory Parameters	24 months	Months 1–24	Conduct alongside recruitment; includes demographics and clinical variables.
d. Data Collection and Documentation	24 months	Months 1–24	Parallel with patient follow-up; capture all required variables.
e. Patient Monitoring and Follow-up	36 months	Months 1–36	Ensure adherence to treatment; monitor side effects and clinical outcomes.
f. Genotyping and PGx Analysis	24 months	Months 1-24	Targeted genotyping; SNP identification and data processing.
g. Quality Assurance	36 months	Months 1–36	Monitor adherence to protocol, sample integrity, and data accuracy.
h. Statistical Analysis and Data Interpretation	12 months	Months 25–36	Perform final analyses; correlate PGx results with clinical outcomes.

8.2 Informed Consent

a. Before entering the studies, each patient will be given oral and written information and written informed consent (Arabic/English), participant will be provided with sufficient time to give their decision on participation at least 48 hours. Patients who are unable or refuse to give informed consent will be excluded.

b. The eligible participant will be enrolled participants will remain in the study for 12 weeks according to the study timeline.

c. The participants will be screened for their eligibility following the clinical diagnosis by a psychiatric physician with MDD or schizophrenia then they will be given all the information to help the participant decide if he wants to be in this study by the research team, the planned screening number is 500 participants.

c. At the time of clinical visit, the participant will be invited to read the consent form carefully before deciding whether you want to take part. The information will also be discussed with the participant by the research team. If there is anything the participant does not understand about this study, he or she can ask the doctor and/or the research team any questions before he makes his/her decision.

d. Participants will not be compensated for their participation in this research study.

8.3 Subject Withdrawal/ Withdrawal of Consent

A subject may be withdrawn from the study by the PI in case of revealing an unexpected adverse effect or develop a serious medical condition. Additionally, the subject can be withdrawn from the study if he is not adherent to the scheduled visits of follow up

8.4 Risk

The study doesn't have any a potential risk. However, team member will report any accidental medical condition, and extensive medical assessment will be provided.

Genetic information is highly sensitive, and the research team will implement maximum-security measures to protect the participants' genetic data. There are a few approaches that link the genetic information back to the person's identifier. There are a number of potential risks with the advances in genomic research including the development of new methods to link the genetic material to the person's identifiers, risks to certain medical conditions that cannot be predicted at the time of conducting the research, and the results of the current research might be different in the future with more research outcomes related to the subject.

Participants would be provided with a point-of-contact in case they have any queries or concerns of any kind during the study.

8.5 Bio-Specimens & Sample Collection

Patients who agreed to participate in the study will be asked to provide a 2 ml Saliva sample for DNA extraction and further genotyping. A coded saliva sample will be stored in Store at **4°C (refrigerator)**until being shipped to QPHI.

The patient will be given written oral information regarding the study before initiation of the study. If the patient decides to withdraw from the study his/her bio-specimen will be destroyed. However, proceeded data will be kept in records

8.6 Admission, transfer, discharge

- Before admission, patients are screened for eligibility as per preidentified inclusion/exclusion criteria.
- Once study team confirm eligibility for the study, participants are invited to sign an informed consent form with unique study ID
- Once the participant completes the protocol of treatment as stated, final data and adverse effects are documented
- All procedures are documented and reported in collection sheets

8.7 Outcomes

- Improvement in patient clinical outcomes and medication tolerance within 4–12 weeks among psychiatric patients prescribed antidepressants or antipsychotics, as a result of genotyping-guided prescribing and PGx testing
- Assessment of the impact of gene-drug interactions on treatment decisions, medication adjustments, and overall pharmacotherapy outcomes

8.8 Data Collection, Management & Confidentiality

a) Please indicate below HOW study data will be collected for the proposed research.

☒ *Study Forms* ☐ *Study Database* ☐ *Study Web-Based/App* ☐ *Other*

a. Data collection sheet will be prepared to collect data regarding patient characteristics (Age, weight, gender, past medication history, …..etc)
b. Clinical outcome data will be collected using the Cerner system of the HMC and stored in files in PI site
c. Genomic data will be collected after sequencing and stored in a secure service in QBB with controlled access only to authorized persons.
d. Data and saliva samples will have a specific code by independent investigators and this code will be further used through the data collection procedure.
e. Genomic data will be stored in a closed online system with secure code. The granted access to the data and well document procedure is in place in QBB (ISO/IEC 27001 information security management).
f. The Principal investigator is the one who has full access to the study data. And study teams will be allowed to acess the coded data for the purpose of analyses.
g. Data will be collected and de-identified and codes will be used to cover patients' identifiers such as Name, HC no. and DOB. The link between the code and the identifier will be destroyed once the study finishes and de-identified data will be stored for at least five years.
G. QPHI/QGP will be responsible for the study procedure, genotyping analysis, data analysis and validation of procedure and data profiling
D. Subject identifiers will not be shared outside HMC. Only de-identified, coded data will be shared with the QPHI team. The QPHI team will receive a coded link between the genetic data and the clinical data without access to direct personal identifiers. This linkage is intended to support physicians in making clinical decisions based on the integration of genetic information with clinical profiles.
The key linking participant identifiers to study codes will be securely maintained within HMC by the principal investigator and designated study team members

9. Study monitoring/Data Safety Monitoring Board (DSMB)

N/A

10. Statistical Consideration and Data Analysis

- Deviation from Hardy–Weinberg equilibrium (HWE) for polymorphisms will be checked using a chi-squared test with one-degree of freedom.
-Continuous data will be expressed as mean ± standard deviation (SD)whilst categorical data will be expressed as percentages. All statistical analyses will be performed using the STATA program and Golden Helix SNP & Variation Suite for genetic analysis.
- A univariate analysis followed by multivariate Cox proportional hazards will be performed to investigate the influence of baseline risk factors.
A 2-sided likelihood ratio test will be used to calculate the P value.
- Hazard ratios are reported with 95% CIs.
- The proportional hazards assumption will be investigated by testing the interaction between treatment groups and the -logarithm of follow-up time. When the assumption is violated, a post hoc analysis will be undertaken to estimate the treatment effect over different segments of the follow-up period.
- The time segments are chosen based on the clinical importance of these periods.
- The relationship between gene variants and the outcome will be also evaluated.
- A statistical analysis plan will be developed prior to any data analysis and missing data will be handled and minimized as possible.

11. Adverse Event Reporting

- All adverse drug reacrtions are reported in accordance to the regulatory guideline per p[rotocol guideline

12. Ethical Consideration

The study will be conducted in full conformance with principles of the “Declaration of Helsinki”, Good Clinical Practice (GCP) and within the laws and regulations of MoPH in Qatar.

13. Sponsor, Funding & Collaborator Information

Qatar Genome Project (QGP)/ QPHI as a member of Qatar Foundation (QF) will will provide co-support for this project in collaboration with HMC. Their support will include facilitating genetic testing, generating genetic data, and contributing to the analysis of the resulting data.

14. Dissemination of Results and Publication policy

a. Scientific Publications and presentations

- The main dissemination task is that the partners of the project will participate in the transfer of the findings and knowledge to the scientific community through the publication of scientific research papers in highly impacted journals. The targeted scientific journals are Pharmacogenomics Journal and Clinical Pharmacology and Therapeutic Journal.

b. Global or regional conferences

- We are going to present our data at different regional and global conferences which can be crucial for diffusing results, particularly early results. Participation in scientific conferences will allow us to receive feedback and spread awareness of the project in the community

15. References

Please cite the sources of all reference materials used to support the hypothesis

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16. Appendices

Supplemet 1: Glasgow Antipsychotic Side-Effect Scale (GASS)

Supplemet 2: Antidepressant Side-Effect Checklist (ASEC):

Research consent form

Data Collection sheet