Towards Implementation of Pharmacogenomics-guided therapy in Patients with Mental Illness

St Vincent's Hospital Sydney

St Vincent's Clinical Genomics &

Departments of Psychiatry, Clinical Pharmacology, Pharmacy

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Responsibilities: Stage P implementation

Study Title	**Implementation of Pharmacogenomics (PG)-guided therapy in Patients with Mental Illness**
Objectives	**Stage P (Preliminary) objectives** Evaluate retrospective file data of patients participating in PG testing and to re-contact patients and their GPs/clinicians to assess the impact of PG testing both on treatment options and patient reported outcomes. **Stage 1 objectives** To evaluate clinician knowledge and acceptability of PG testing and resource needs to inform mainstream implementation of PG. Overall objectives To develop a Model of care (MOC) which will be utilised in Stage 2 and evaluated in stage 3 (note stage 2 and 3 will be a separate protocol)
Study design	Mixed 2 stage design – observational, qualitative, and quantitative components
Planned sample size	**Stage P** Up to 100 retrospective files to be reviewed Participants will be contacted via email to discuss their experiences of PG testing. The email will contain a survey link. Up to 100 clinician surveys. It is anticipated that most of the clinicians will be General Practitioners. **Stage 1** **Interview 1- Clinician** Psychiatry Physicians n=10 Pharmacist n=10 **Survey 1- Clinician** Psychiatry Physicians n=10-20 Pharmacist n=10-20
Selection criteria	**Stage P** Adult patients aged 18 years or over, who have previously undergone PG testing through St Vincent's Clinical Genomics (SVCG) GPs/clinicians involved in the care of these patients who previously had testing **Stage 1** Clinicians in Departments of Psychiatry and Pharmacy of SVHS who have given implied consent by agreeing to participate in interview/survey

Study procedures	**Stage P** (1) A retrospective audit of pharmacogenomics results of patients who underwent testing as part of their routine clinical care at the SVCG (up to 100 patients) (2) Survey of GPs/clinicians (up to 100) involved in the care of patients who had PG testing as part of their routine care (*Clinician Survey P*) (3) Survey of patients who had PG testing as part of their routine care. Evaluate their knowledge of PG results, as well as how the PG testing has impacted their pharmaceutical care and overall mental and physical health (*Patient Survey P*) Outcomes from Stage P will be used to inform and refine interview/survey questions for Stage 1. **Stage 1** In order to develop a model of care (MOC) and resource needs of clinicians in regards to clinical implementation of PG testing, clinician's knowledge, perceived utility and acceptability of this need to be evaluated. These parameters will be evaluated by conducting, first, interviews with Psychiatry physicians and clinical pharmacists (Clinician Interview 1), followed by surveys which aim to capture a broader perspective from within Departments of both Psychiatry and Pharmacy (*Clinician Survey 1*).
Statistical considerations	Sample size calculation is not applicable as both Stage P and 1 utilise a qualitative methodology. Quantitative data from surveys will be reported in descriptive terms. Analysis plan
Study duration	8 months (2 months for Stage P retrospective data review and 6 months for Stage 1)

Contents

1.BACKGROUND

1.1. BACKGROUND*

Genetic factors play an important role in contributing to the variability in response to pharmacological agents. For example, genetic variants can affect the activity of enzymes involved in drug metabolism, either reducing or enhancing drug exposure and thus altering drug response and toxicity profiles.(1)

The evidence behind such drug-gene interactions (DGIs) and their effect on drug response/toxicity is well established. Positive benefit-risk ratios have been demonstrated by randomised controlled trials evaluating the associations between CYP2D6, VKORC1, TPMT, HLA-B*5701 and their respective drug responses.(2) As of June 2017, the Clinical Pharmacogenetics Implementation Consortium (CPIC)(3) has published 33 clinical practice guidelines covering 36 drugs and 14 genes. Furthermore, more than 150 US Food and Drug Administration approved drugs also report genotype information on their labels, many in conjunction with recommended dosage modification or alternative medication.(4)

Pharmacogenetics is the study of how genetic variants affect an individual's response to a drug. Leveraging recent advances in sequencing technology, pharmacogenomics (PG) testing can simultaneously screen for multiple high-evidence genetic variants that alter response to each of the currently known 300+ medications with actionable drug-gene interactions based on CPIC(3) curated evidence. PG is applicable to all areas of medicine, and represents a significant enabler to Precision Medicine, providing the ability to tailor medication choice and dosing based on each individual's genetic makeup. The potential utilities of PG-guided pharmacotherapy include reduction in adverse drug reactions, minimisation of side effects, and avoidance of non-therapeutic response.(5)

PG-guided therapy has been shown to significantly enhance clinical outcomes in the field of mental health. Currently, two-thirds of patients with a major depressive disorder fail to achieve remission during the first treatment level(6); and many require multiple different medications sequentially on a trial-and-error basis(7). In addition, it has been shown that the odds of remission diminish with every additional medication trial-and-error;(6) and that a window of therapeutic opportunity for major depressive disorder appears to be within the first 2 sequential treatments.(8) PG-guided pharmacotherapy, which aims at giving the right drug at the right dosage to the right person at the right intervention time, has the potential to improve both patient outcomes and health cost savings in the Mental Health system.

Several large randomised controlled trials comparing PG-guided treatment versus conventional treatment based on clinician judgement, in patients with Major Depression +/- Anxiety, have shown better clinical outcomes, including significantly improved rates of response (by 4-5 folds) and remission (by 2-3 folds), and better medication tolerability/adherence, in the PG-guided treatment group vs control.(9-12) Indeed, one study reported that the number needed to genotype was 3 (95% CI 1.7 – 3.5).(9) Furthermore, PG-guided psychotropic treatment has been shown to reduce medication costs and lead to overall cost savings compared to conventional treatment.(13-15) For example, one study investigating the pharmacy claims of 13,048 psychiatric patients, over 12 months post-PG testing in the intervention group versus control, reported an average cost saving of US$2,774.53 per patient per year and better medication adherence.(13) Similarly, another study reported that PG-guided treatment of patients with severe depression had an incremental QALY gain of 0.49 and cost saving of US$6,800/patient/year compared with patients receiving conventional treatment.(14)

1.2. RATIONALE FOR PERFORMING THE STUDY*

Despite the evidence, Australia has been slow in adopting PG testing to guide therapy. Indeed, a recent Australian Parliamentary Inquiry into the Management of Healthcare Delivery in NSW, in its published Report 8/56 in September 2018, expressed concerns that PG testing is not being adequately utilised in the public mental health system. It further identified PG testing as one of the key mental health priorities and made recommendations that NSW Health actively pursues and funds the increased use of PG testing as a means of improving treatment for patients with mental illness.(22)

Before widespread clinical implementation of PG testing, the best practice is to develop a model of care (MOC), which in turn will be informed by the attitudes and acceptability of PG, as well as the support and resource requirements, amongst potential end-users, including clinicians and patients. A well-informed MOC will enhance the feasibility and clinical utility of PG testing to ensure successful implementation of PG guided pharmacotherapy into routine clinical care of patients with mental illness.

Overall, while there is a growing interest in PG testing amongst patients (23), the adoption and usage of PG among clinicians/pharmacists are less certain.(24) Several studies in the US have identified the lack of knowledge, and the lack of decision-aid support, as the main barriers to clinician acceptance.(25-30) Although this view was similarly shared by Australian clinicians/pharmacists several years ago(30-32), no recent studies have investigated the attitudes, acceptance, and support needs of Australian patients and clinicians regarding PG testing. A renewed understanding of the potential barriers to PG implementation and support needs of the end-users from the Australian Healthcare perspective will help inform future policy making, both at the hospital level and the health policy level.

STUDY OBJECTIVES*

1.3. PRIMARY OBJECTIVE*

To be the first centre in Australia to develop, implement and evaluate an innovative model of care (MOC) to incorporate evidence-based PG-guided therapy for patients with mental illness, with an aim to improve the clinical care and outcome of this vulnerable patient population.

This project proposal is comprised of four stages (current protocol stage P and 1 with a separate follow on protocol for stage 2 and 3), with the following objectives, which aim to ultimately change routine clinical practice in the management of patients with mental illness.

STAGE P

Evaluate retrospective file data of patients participating in PG testing carried out in St Vincent's Clinical Genomics. The PG testing is not limited to those related to mental health concerns. This stage will assess the impact of PG testing both on treatment options and patient/clinician reported outcomes.

STAGE 1

To change routine clinical practice, by developing a MOC and its implementation plan, for PG-guided psychotropic therapy in patients with mental illness within the St Vincent's precinct. To best inform MOC development, it is important to understand the prescriber's attitudes, acceptability, and knowledge of PG testing, and the resource needs for clinical implementation, as well as to examine how the PG information will be utilised in the immediate and short-term periods.

The data generated from the overall study comprising of Stage P and 1 (this protocol) and extension protocol (separate stage 2 and 3 protocol) will form the basis for future research grant applications to examine the cost-effectiveness of PG-guided treatment in Mental Health, with a longer-term goal of influencing the Australian health policy including lobbying for Medicare rebate for PG testing in this vulnerable patient population.

2. STUDY DESIGN*

2.1. DESIGN*

Mixed methodology with observational/qualitative and quantitative methods

2.2. STUDY GROUPS*

Stage P Retrospective file review and patient and clinician surveys

Stage 1 Psychiatrists and pharmacists at St Vincent's Hospital Sydney

2.3. NUMBER OF PARTICIPANTS*

Stage P

Up to 100 Participant files for retrospective chart review. All patients will be contacted via an email invitation.

Stage 1

20 clinicians in Psychiatry

20 Clinical pharmacists

2.4. NUMBER OF SITE

Single site at St Vincent's Hospital Sydney

2.5. DURATION

Stage P- 3-6 months

Stage 1- 6 months

3. PARTICIPANT SECTION

3.1. INCLUSION CRITERIA*

Patient re-contact (Stage P):

- Adult patients aged 18 years or older
- Previously had PG testing arranged through SVCG
- Understands spoken and written English
- Willingness to give implied consent, and willingness to participate in and answer specific survey questions

Clinician (Stage P):

- Registered clinicians involved in the current care of the patients who had PG testing
- Willingness to give implied consent, and willingness to participate in and answer specific survey questions

Clinician (Stage 1):

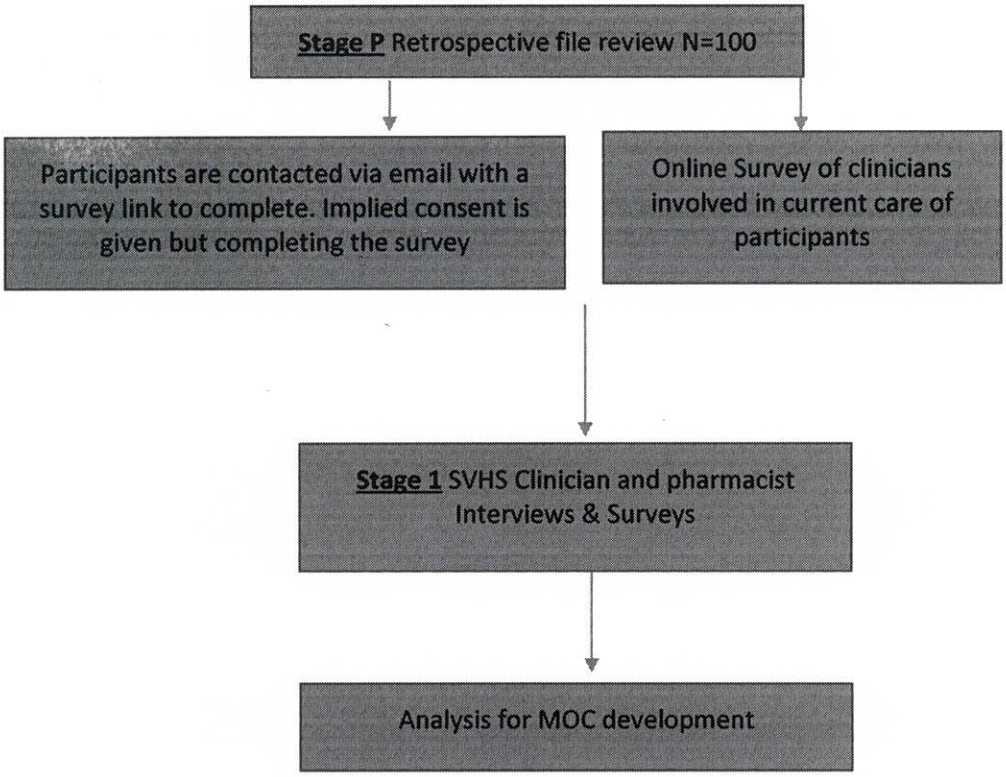
- Clinicians, including specialists, registrars, residents, and clinical nurse consultants/practitioners, who are employed by the Departments of Psychiatry and Pharmacy at St Vincent's Hospital Sydney (SVHS)
- Willingness to give verbal consent, and willingness to participate in and answer specific interview/survey questions

3.2. EXCLUSION CRITERIA

Unwilling to participate in study

4. STUDY OUTLINE*

4.1. STUDY FLOW CHART



4.2. INVESTIGATION PLAN*

Methodology

Stage P

Retrospective chart review of patients who underwent PG testing at SVCG between 1 July 2018 and 31 August 2019, to determine:

- Average number of high-risk drug-gene interaction (DGI)
- Average number of moderate-risk DGI
- Number of genetically incongruent medications each patient is currently taking
- Average number of genetically incongruent medications that are currently taken by patients
- History of medication side effects/adverse drug reactions
- Event of medication side effects/adverse drug reactions attributable to DGI

Re-contact of patients & patient interview

Patients who were previously seen for PG testing at SVCG will be emailed an information sheet about the study and a survey link (*Participant Survey P)*. The survey asks specific questions, and their answers will be compiled, for qualitative analysis. Redcap will automatically assign a ID code to enable the participant responses be linked to the records. No identifiable data will be sent off site so participate details will remain confidential. A master list of those participant contacted will be kept securely in the SVCG.

Clinician interview

The clinicians involved in the current care of patients who underwent PG testing will be contacted via email and invited to complete an online survey *(Clinician Survey P).* The email will also contain information about the study. Those clinicians who do not return the survey will be contacted by telephone to discuss further. The survey will contain re-identifiable information but will later deidentified for qualitative analysis. A set of survey questions are provided.

STAGE 1 (Development of MOC and implementation plan)

Mixed methods combining qualitative (one-on-one interviews) and quantitative (surveys) methodologies will be adopted in order to gain a wide range of perspectives from potential users of the PG guided treatment service, across St Vincent's Hospital Sydney (SVHS).

1a. One-on-One Telephone Interviews

Approximately 10 clinicians in Psychiatry (including key opinion leaders in department, nurse specialists and care coordinators) and 10 pharmacists at SVHS will be recruited to participate in semi-structured telephone interviews (*Clinician Interview 1*), until data saturation as per grounded theory qualitative research. Interview questions may include current practices regarding prescribing medications, and aims to explore the knowledge, understanding, perception, attitudes, acceptance, concerns and perceived utility of PG as well as the support needs for implementation.

1b. Survey

Quantitative data will be collected from all psychiatrists and pharmacists via a once-off survey (*Clinician Survey 1*), designed based on the qualitative data collected. This aims to capture a wider range of perceptions to inform the optimal model of care for implementation of PG in Psychiatry.

4.3. Study Procedure Risks*

There are no foreseen risks to this study.

4.4. Recruitment and Screening*

Stage P

Retrospective audit of medical records

- Patient recruitment for survey: The research officer will review SVCG patient records to identify potential participants who have previously undergone PG testing at St Vincent's Hospital. Participants will be emailed with information regarding the research project. The email will contain a link to the survey. By completing the survey the participants are giving implied consent.
- Clinician survey: Clinicians involved in the current care of the patients who had PG testing will be contacted via email and invited to return the online survey

Stage 1

- Clinicians, including specialists, registrars, residents, and clinical nurse consultants/practitioners, who are employed by the Departments of Psychiatry and Pharmacy at St Vincent's Hospital Sydney will be invited to participate in phone interview and/or survey. Information about the research and the objectives will be emailed along with a formal invitation to participate.

4.5. INFORMED CONSENT PROCESS*

Stage P

Retrospective data review.

All participant medical records that are reviewed will be re-identifiable so there will be no confidentiality issue. Participants will be contacted via an email invitation. Due to the nature of the study it is not feasible or essential that the participant is seen in person. The email will contain information about the study and a link to an online survey for them to complete. By completing the survey is giving consent as per national Statements section 2.2.5 on implied consent. The decision whether to complete the survey or not will have no impact on their future care at St Vincent's Hospital. All participant details will be de-identified in a re-identifiable format with the master list kept securely.

Clinicians involved in the care of those who have received PG testing will be invited via email to complete the survey. The email invitation will contain an individual study ID code that will be re-identifiable. The master list will be kept securely with the coordinating investigator. If the clinicians do not wish to participate they will be asked to email to opt out of the survey. By returning the survey is giving consent as per national Statements section 2.2.5 which discusses implied consent. For those who did not opt out and did not return the survey, they will be contacted by phone to discuss further.

Stage 1

1a. One-on-One Telephone Interviews

Clinicians in Psychiatry and Pharmacist will be contacted via email with an information sheet explaining the study. They will be asked to email if they do not wish to be contacted to participate. Those who did not opt out will be contacted via telephone for an interview. By agreeing to conduct the interview, the clinician gives their consent for participation. Clinicians will be able to decline the interview with no affect to their relationship to the researchers. The SC will assign an individual re-identifiable study ID code. The master list will be kept securely with the coordinating investigator.

1b. Survey

All psychiatrists and pharmacists, including trainees, allied health and nurse practitioners, will be contacted via email with an information sheet explaining the study as well as a link to the online survey. The email invitation will contain an individual study ID code that will be re-identifiable. The master list will be kept securely with the coordinating investigator. By returning the survey is giving consent as per national Statements section 2.2.5 which discuses implied consent.

4.6. ENROLMENT PROCEDURE*

Stage P

Participant medical records will be reviewed and if meets inclusion criteria, data will be recorded under a re-identified study number.

Those participants and clinicians who are contacted and who give implied consent will be enrolled.

Stage 1

Clinicians will be enrolled into the study once they have reviewed the information and agreed to participate and verbal consent has been obtained.

5.SAFETY*

Some participants may find some of the questions confronting. They will be advised to seek counselling if required

5.1. ADVERSE EVENT REPORTING*

There are no safety concerns in relation to this study.

5.2. DATA SAFETY AND MONITORING BOARD

A DSMB will not be convened for this study. It is not foreseen that there will be any safety concerns

5.3. EARLY TERMINATION

In the unlikely event that this study is terminated early, the Principal Investigator (or one of the Co-investigators if PI is unavailable) will notify the participants and the HREC in writing, and compile a final study report

6.OUTCOMES AND FUTURE PLANS

Data from Stage P and 1 will form the base for further research (Stage 2 and 3) into an innovative model of care (MOC) to incorporate evidence-based PG-guided therapy.

This project will be the first in Australia to develop (Stage P and 1), implement (Stage 2), and evaluate (Stage 3) an MOC with an aim to improve the clinical care and outcome of this potentially vulnerable patient population.

Data from this study will further form the basis for future research grant applications to examine the cost-effectiveness of PG-guided treatment in Mental Health, with a longer-term goal of influencing the Australian health policy including lobbying for Medicare rebate for PG testing in this vulnerable patient population.

7.STATISTICAL CONSIDERATIONS*

A power calculation on sample size is not applicable for the current study as this is predominantly an observational/qualitative study.

8.CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS*

All data generated from file review, as well as surveys and interviews in both Stage P and Stage 1 will be stored electronically in a re-identifiable format. The data will be securely stored electronically on the SVCG server and password protected with access limited to research personnel.
All data stored will be kept for a minimum of 15 years as per ICH GCP, from the date of publication, in accordance to the minimum recommended period for retention of research data stated in section 2.1.1 of the NHMRC Code for Responsible Conduct of Research (10). After this period, electronic data will be permanently deleted, and paper documents will be securely shredded.

9.OTHER STUDY DOCUMENTS

- Retrospective file review Excel data collection sheet
- Email Invitation – Stage P Clinician Survey Information Sheet
- Email Invitation - Stage P Patient Survey information sheet
- Email Invitation – Stage 1 Clinician Interview Information Sheet
- Email Invitation – Stage 1 Clinician Survey Information Sheet
- Clinician Survey P
- Patient Survey P
- Clinician Interview 1
- Clinician Survey 1

10.RESOURCES

This study is kindly funded by the Inclusive Health Program Grant 2018/19.

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