Determining the Feasibility, Acceptability, and Preliminary Effectiveness of PGx Testing in Primary Care

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Abstract

Background: Antidepressants are commonly prescribed by primary care providers for treating depression, anxiety, and other conditions. A trial and error approach is typically used to identify effective therapy. Treatment efficacy and safety of many antidepressants can vary based on the presence of certain diseases and metabolism gene types. Pharmacogenomic (PGx) testing provides phenotypic classification of individuals as poor, intermediate, extensive, and ultra-rapid CYP450 metabolizers. This allows more accurate drug selection for efficacy and dosing to minimize toxicity.

Objective: To determine the preliminary effectiveness of PGx testing for selection of effective antidepressant, medication adherence, depressive symptoms, and healthcare utilization. To determine acceptability of PGx testing in primary care among patients and providers.

Methods: This is a 6-month randomized, wait-listed, controlled pilot trial conducted in 6 department of family medicine (DFM) clinics at the University of Michigan (UM). We will enroll physicians practicing at a UM DFM clinical site who are willing to utilize PGx test results in conjunction with treating patients prescribed certain antidepressants. We will also enroll patients of these DFM physicians who are adults with a new prescription for an antidepressant (within the past 4 weeks) including patients who have switched to a new antidepressant from another antidepressant or have added on a new antidepressant to current antidepressant therapy. Patients are excluded if taking an antidepressant for more than 4 weeks and if they have had PGx testing in the past.

Physician participants will complete a baseline survey to assess demographics, and knowledge, acceptability and utility of PGx testing for this population. At the conclusion of the study, physician participants will complete a semi-structured interview to assess knowledge, satisfaction, feasibility, acceptability, effectiveness, barriers to widespread adoption, and utility of PGx testing.

All patients will complete a baseline, 3-, and 6-month assessment; control patients will have an additional 9-month assessment. Data to be collected include reasons for antidepressant use, depression and anxiety symptoms and severity, functional health status (SF-12), PGx knowledge, work status changes, demographic information, physician and emergency department visits, adverse effects, and medication alterations and adherence.

Contents

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2.0 Introduction

According the Centers for Disease Control and Prevention, between 2011 and 2014, 10.7% of Americans reported taking at least one antidepressant in the past month. [1] Antidepressants were the third most commonly used medication after cholesterol and pain medications. Antidepressants are prescribed for the management of depression, anxiety, and other conditions. Given that the time from initiation of pharmacologic treatment to clinical effect takes two to four weeks,[2, 3] coupled with the fact that the initial medication may not be effective, thus necessitating adjustments to dosages or medications, treatment with an antidepressant can be a long and complicated process, during which patients still experience symptoms. Strategies to improve treatment often include switching patients to a different antidepressant or prescribing an additional antidepressant.[4]

One reason for poor response to antidepressants can be attributed to the drug metabolism process. Many of the most commonly prescribed antidepressants undergo phase one xenobiotic metabolism by a class of enzymes in the P450 superfamily. This family of enzymes exhibits a high degree of genetic polymorphism, resulting in variable metabolism. Because of this variation in P450, we can classify individuals as poor, intermediate, extensive, and ultra-rapid metabolizers. The consequence of this population heterogeneity is that medications are metabolized at different rates and plasma concentrations of specific drugs can be outside of the optimal range, which may result in adverse drug events or lack of therapeutic effect. Because of these two medication outcomes, treatment may be discontinued.

Pharmacogenomic (PGx) testing of several cytochrome P450 genes and the most frequently described functional variants (CYP2D6, CYP2C9, CYP2C19, and CYP1A2) can be used to predict the metabolic capacity of an individual. For example, it is estimated that 5-10% of Caucasian individuals are poor metabolizers and 1-2% are ultra-rapid metabolizers based on CYP2D6 phenotypes.[5] By knowing a patient's genetic information and the drug's major metabolic pathway, we can prospectively assess the appropriateness of specific medications, modifying the dosing or using enhanced monitoring. By identifying the approximately 10% of individuals who will not metabolize antidepressants properly via the CYP2D6 pathway, we may be better able to identify effective treatment options and minimize adverse effects.

While the promise of this personalized medicine approach has been high, clinical uptake of PGx testing has lagged behind due to a combination of factors, including but not limited to provider confusion, lack of expertise, lack of studies confirming clinical utility, cost of testing, and a lack of an integrated approach.[6]

3.0 Objectives

PGx testing could greatly improve the use of antidepressants by aiding prescribers in identifying proper medications for individual patients; thus potentially improving medication adherence, as well as reducing symptoms and antidepressant side effects.

This pilot study will explore the use of PGx testing in primary care, and is guided by several specific aims:

Specific Aim 1: To determine the effect of PGx testing on the primary outcome of physician treatment decisions, as measured by the change in the proportion of patients who are prescribed medications at baseline that are contraindicated according to the PGx test, compared to the proportion at six-month follow-up.

Specific Aim 2: To determine the effect of PGx testing on secondary outcomes measures of interest, including change in symptoms and severity and medication adherence from baseline to six-month follow-up.

Specific Aim 3: To determine the acceptability of PGx testing in primary care among patients and physicians.

4.0 Resources and Personnel

4.1 Setting

This study will be conducted with physicians and patients recruited from the University of Michigan (UM) Department of Family Medicine (DFM), which has six clinical sites; Briarwood (Ann Arbor), Domino's Farms (Ann Arbor), Ypsilanti, Chelsea, Dexter, and Livonia.

4.2 Staff Roles and Responsibilities

	Buis	**Ellingrod**	**Farris**	**Klinkman**	**Ruffin**	**Mitrzyk**	**Kadri**	**Statistician**
Study Design	X	X	X	X	X			
Recruitment						X	X	
Consenting Participants						X	X	
Data Collection						X	X	
Consulting with Physicians on PGx Test Results		X				X		
Access to PHI	X	X		X		X	X	X
Data Analysis	X					X	X	X
Report Preparation	X	X	X	X	X	X	X	X

4.3 External Partners

All blood specimens will be sent for analysis to Progenity, a CLIA-accredited molecular diagnostics laboratory in Ann Arbor, MI. Progenity will provide a report for each sample to the study staff via MiShare or other secure transmission method, who will in turn release the results to physicians, along with any treatment recommendations based on the test results, via MiChart. The arrangement between UM and Progenity is covered by a contract.

5.0 Study Procedures

5.1 Study Design

This study will include two different populations of participants; primary care physicians and their patients who have been recently prescribed and taking one of the following antidepressants: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Prozac Weekly, Rapiflux, Sarafem, Selfemra), fluvoxamine (Luvox, Luvox CR), paroxetine (Paxil, Paxil CR), sertraline (Zoloft), duloxetine (Cymbalta, Irenka), venlafaxine (Effexor, Effexor XR), nortriptyline (Aventyl, Pamelor), bupropion (Forfivo, XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL), mirtazapine (Remeron, Remeron Soltab), or vortioxetine (Trintellix). We will recruit and enroll approximately 30 UM DFM physicians to participate in this study. For physician participants, we will obtain consent and then conduct assessments of baseline PGx knowledge, as well as semi-structured interviews and surveys regarding their experiences at the conclusion of the study. Please see Figure 1 for physician participant study flow.

From those participating physicians, we will recruit 100 of their adult patients who have been newly prescribed one of the antidepressants listed above. These patient participants will be enrolled in a six-month randomized wait-listed control pilot study.

Patient participants will meet with study staff for consent and baseline data collection at a Michigan Clinical Research Unit (MCRU) in either Domino's Farms or the Cardiovascular Center. Once consent and baseline data collection are complete, participants will have their blood drawn by MCRU laboratory staff. A single 4 mL Lavender top EDTA tube of blood will be drawn. Once the blood draw is complete, study staff will send the sample to Progenity for analysis. After the baseline assessment is complete, patient participants will be randomized equally to either have their test results sent immediately to their participating primary care physicians once available, or to have their test results sent in three months. Randomization will be stratified by physician in ten block units to ensure balance by physician. PharmDs on the research team (Ellingrod and Mitrzyk) will be available to consult with physician participants at any time during the study; however, our study PharmDs will meet with each participating physician at least once, when their first patient PGx test results are available to provide general, as well as patient specific education about the PGX test and results. These consultations will help physicians to interpret PGx test results, and may help to guide treatment decisions, if necessary. Study pharmacists or staff will not

provide PGx results to patients; it is up to the patient's physician to provide this information if he/she feels it is appropriate. Likewise, although study pharmacists may make treatment recommendations based on the PGx test results, it is up to the treating physician to decide whether to act on those recommendations. All intervention patient participants will be followed for a total of 6 months, with phone-based follow-up assessments occurring at 3- and 6-months. All control patients will be followed for 9 months, with phone-based follow-up assessments occurring at 3-, 6-, and 9-months. Please see Figure 2 for patient participant study flow.

Figure 1. Physician Participant Study Flow

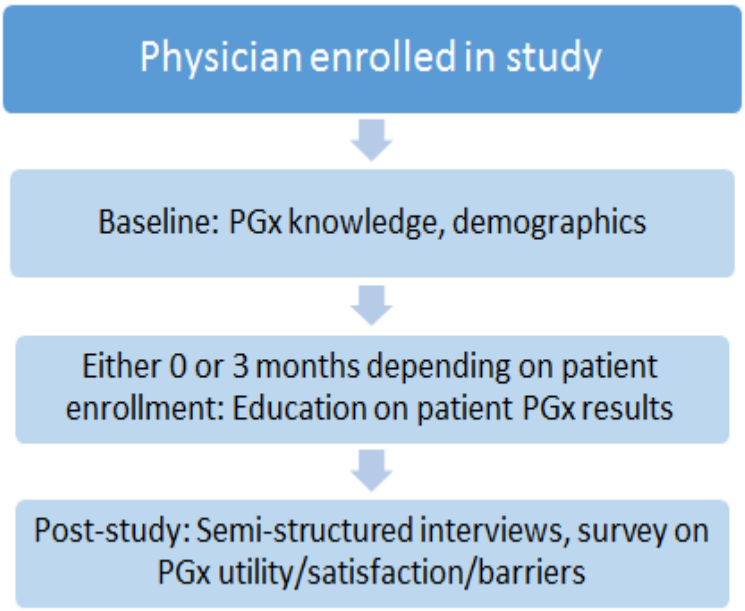
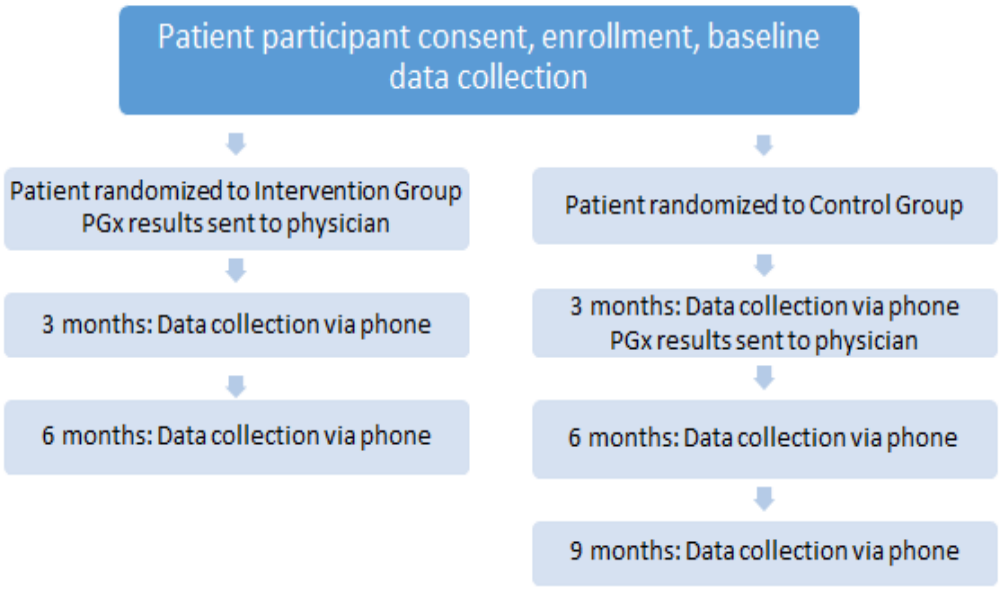


Figure 2: Patient Participant Study Flow



Physicians and patients enrolled in this study will be exposed to minimal risk. Participants in both arms of the study will undergo PGx testing. Physicians for intervention group participants will receive PGx test results as soon as they are available, whereas those participants in the waitlisted control group will receive their test results three months after enrollment. Because the current standard of care does not involve the use of PGx testing, our waitlisted control group is not exposed to any additional risk above and beyond usual care. To clarify, the intervention under investigation in this study is the PGx test. We will not directly intervene in the clinical care of a patient, as all clinical decision making is at the discretion of the physician managing a patient's care. All participants in this study may benefit because their antidepressant medication may be tailored to their pharmacogenomic profile. Although both populations of participants run risks associated with breaches of privacy due to electronic storage of study data, every effort will be made to minimize these risks.

5.2 Recruitment Methods

To conduct this pilot RCT, we will recruit from two populations of participants; primary care physicians, and 100 patients of those physicians who have been newly prescribed a certain antidepressant.

5.2.1 Physician Participants

Physician participants will be recruited through presentations of the study at UM DFM Grand Rounds and faculty business meetings, clinical site staff meetings, and targeted emails and letters to all UM DFM physicians who treat patients.

Study staff may also call providers who have not responded to recruitment letters/emails up to two times. In the event that a potential participant is eligible to participate in the study, except for the fact that their primary care provider is not yet participating, we will attempt to recruit the provider through up to two additional emails and two additional phone calls. Any provider who indicates that they are not interested in participating will not be contacted further. Provider participants will receive no incentives for their participation in this study.

5.2.2 Patient Participants

For patient participant recruitment, once UM DFM physicians have been consented and enrolled, we will recruit their patients who have new prescription for an antidepressant(with the past 4 weeks prior to screening) from the following list: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Prozac Weekly, Rapiflux, Sarafem, Selfemra), fluvoxamine (Luvox, Luvox CR), paroxetine (Paxil, Paxil CR), sertraline (Zoloft), duloxetine (Cymbalta, Irenka), venlafaxine (Effexor, Effexor XR), nortriptyline (Aventyl, Pamelor), bupropion (Forfivo, XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL), mirtazapine (Remeron, Remeron Soltab), or vortioxetine (Trintellix). These potential patient participants will be identified through direct provider referral via flags to providers in MiChart and patient brochures, signs and brochures posted in the UM DFM clinical sites, and targeted recruitment letters, followed by recruitment phone calls, to patients who meet eligibility criteria as identified in MiChart.

To facilitate the delivery of targeted recruitment letters to potential patient participants, we will obtain lists of potentially eligible participants from the Data Office on a rolling basis. Letters will be batched and sent in waves.

To thank patient participants for their participation in this study, we will provide a $20 check after each data collection assessment (up to $60 for intervention group participants, and up to $80 for waitlisted control group participants). All incentives will be pro-rated for partial study completion. Incentives will be distributed by the UM Treasurer’s office through the Human Subjects Incentive Program.

5.3 Informed Consent Procedures

We will obtain written informed consent from both groups of participants in this study (physicians and their patients). First, research staff (including project coordinators and research assistants) will describe the study to physician participants and obtain written informed consent. Once physician participants are consented and enrolled, we will then recruit patients of those physicians who are newly prescribed a certain antidepressant. Research staff (including project coordinators and research assistants) will explain the study to patient participants and written informed consent will be obtained. Any participant who is unable to provide consent for himself/herself will be excluded from this study. Whenever possible, study staff will seek to conduct consent and baseline data collection at the MCRU site in order reduce burden on participants.

5.4 Inclusion/Exclusion Criteria

5.4.1 Physician Participants

To be included in this pilot trial, physician participants must:

- Be a practicing physician at one of the six UM DFM clinical sites
- Be willing to utilize PGx test results to adjust antidepressant therapy for their participants enrolled in the study
- Be willing to allow study staff to contact their patients
- Self-report that they are willing to prescribe antidepressants
- Be at least 21 years old

Physician participants will be excluded from this pilot trial if they:

- Do not meet inclusion criteria

5.4.2 Patient Participants

To be included in this pilot trial, participants must:

- Be a patient of a participating physician
- Have a new prescription for a certain antidepressant recorded in MiChart (within the previous 4 weeks prior to screening)
- Be currently taking the new antidepressant
- Be willing to undergo PGx testing via single tube blood draw
- Be at least 18 years old

Participants will be excluded from this pilot trial if they:

- Do not speak English
- Have previously undergone PGx testing
- Are unable to provide their own consent to participate in the study
- Have been taking the new targeted antidepressant for longer than 4 weeks (prior to screening)

5.5 Study Evaluations

5.5.1 Physician Participants

Physician participants will be screened for inclusion/exclusion criteria prior to consent and enrollment. After enrollment, all physician participants will complete a baseline survey that assesses demographics and participant characteristics, knowledge of PGx testing, as well as perceptions of the acceptability and utility of PGx testing in primary care. At the conclusion of the study, physician participants will complete a semi-structured interview and survey that will assess

knowledge of PGx testing, whether they recommended PGx testing to other physicians, or ordered PGx testing on patients not included in this study; as well as perceptions of the feasibility, acceptability, effectiveness, and utility of PGx testing in primary care, including barriers to widespread adoption, as well as satisfaction. Surveys/interviews will be audio recorded when permitted by participants. Please see Table 1 for physician participant measures and timing of assessment.

Table 1: Physician Participant Measures

Construct	Measure	Assessment Time	
		Baseline	Post-Study
Demographic information and characteristics of physicians	*Investigator Developed Semi-Structured Interview and Survey*	X	
Knowledge of PGx testing		X	X
Acceptability of PGx testing		X	X
Utility of PGx testing		X	X
Effectiveness of PGx testing		X	X
Feasibility of PGx testing		X	X
Barriers to PGx testing		X	X
Satisfaction with PGx testing		X	X

5.5.2 Patient Participants

Patient participants will be screened for inclusion/exclusion criteria prior to consent and enrollment. After enrollment, all patient participants will complete a baseline, 3-, and 6-month assessment. Control patients will have an additional 9-month assessment of the previously mentioned items. All baseline data will be collected via paper forms and then transferred into REDCap, whereas 3-, 6-, and 9-month assessments will be conducted via phone and entered directly into REDCap by study personnel. The constructs, measures, and data collection times are shown in Table 2. In addition to these measures collected during data collection visits, data will be extracted from MiChart to document treatment, including medication changes, and healthcare utilization for patient participants during the study. We will also extract any available PHQ-9 and GAD-7 data, which is now collected as a part of routine clinical practice. Surveys/interviews will be audio recorded when permitted by participants.

Table 2. Patient Participant Measures

Construct	Measure	Assessment Time			
		Baseline (via paper survey)	3 months (via phone)	6 months (via phone)	9 months (Control Only; via phone)
Reason antidepressant was prescribed		X	X	X	X
Depression Symptoms and Severity	Personal Health Questionnaire Depression Scale (PHQ-8)	X	X	X	X
Anxiety Symptoms and Severity	Generalized Anxiety Disorder 7-Item Scale (GAD-7)	X	X	X	X
Functional Health Status	12-Item Short Form Survey (SF-12)	X	X	X	X
PGx Knowledge	*Investigator Developed*	X			X
Missed days of work	Work Productivity and Activity Impairment Questionnaire (WPAI)	X	X	X	X
Demographic information		X			
Health history	Smoking history, BMI	X			
Healthcare utilization	Physician visits, hospital and ER admissions	X	X	X	X
Adverse Drug Reactions	Antidepressant Side-Effect Checklist (ASEC)	X	X	X	X
Medication and medication changes	Medications prescribed and number of medication changes	X	X	X	X
Medication Adherence	Adherence to Refills and Medication Scale (ARMS)	X	X	X	X
	Pill count	X	X	X	X
	Three-Item Self-rated Adherence Scale	X	X	X	X

5.6 Data Analyses

In this study, we expect to enroll up to 30 physician participants and expect a retention rate of 90-100%. We also expect to enroll about 100 patient participants and expect a retention rate of 80% at the completion of this study.

Data from this study will be analyzed by the study statistician. Survey data will be analyzed using descriptive statistics. Multiple-choice questions will be analyzed using standard quantitative techniques including Chi square and t-test. Open-ended responses will be independently coded using qualitative methods, including any transcripts that result from the recorded survey responses.

Independent sample t-tests will be used to compare outcomes between intervention and control groups at each time point, as well as at similar time points after test results were released to physicians (i.e. baseline for intervention vs. 3 month for control group). Linear mixed models will assess the change in outcomes, as well as whether the change is similar between groups. This will be done by including time, study group, and a time by study group interaction as predictors of each outcome. Time will be considered in two ways, first as the time in study, and secondly as time since test results were released to physicians. In the latter, only data from 3-month to 9-month will be included for the control group, and baseline to 6-month for intervention group, due to timing of test result release. Models will be adjusted for patient demographics.

5.7 Withdrawal of Subjects

Participants may be withdrawn from the study without their consent if the PI feels that it is unsafe for the participant to continue to participate, or if they refuse the blood draw. Participants may withdraw from the study at any time by contacting study staff either in writing or by calling the study hotline.

6.0 Project Timeline

	Year 1 – 2016		Year 2 – 2017				Year 3 – 2018			
	(quarter)		(quarter)				(quarter)			
	3	4	1	2	3	4	1	2	3	4
Protocol development, IRB approval, personnel hiring/training	X	X								
Contracting with Progenity		X								
RCT recruitment and enrollment			X	X	X	X	X	X		
RCT data collection (9 month follow-up)							X	X	X	
RCT data analysis										X
Final report preparation										X

7.0 Reporting

Participants will be requested to call the study hotline to report any adverse events (AEs) or unanticipated problems. All staff will be directed to report any serious (SAEs), protocol deviations, and unanticipated problems to the Project Coordinator as soon as possible. The Project Coordinator or the PI will submit the appropriate documentation to the UM IRB or other department as required.

8.0 Privacy and Confidentiality

This study will utilize PHI including the following elements: name, date of birth, full mailing address, clinic dates, phone numbers, email addresses, social security numbers, medical record numbers. All study staff-generated electronic study data including participant identifiers will be securely maintained in REDCap, or a UM restricted server, in an access-limited folder, with access given only to specified project staff. All participants will be assigned a study ID, which will be associated with their survey data. Although we will maintain a file that links patient MRN and study ID, this will be kept separate from other study data, in a manner consistent with UM policies for PHI. The results of the Progenity Informed PGx tests will be transmitted back to study staff via secure means such as MiShare and stored securely in access-limited folders. All paper records and audio recordings and equipment with patient identifiers will be kept in a locked office, in locked file cabinets. Access to the file cabinets will be restricted to approved study personnel.

PHI sent to Progenity as part of ordering the PGx test is protected as required by the contract.

9.0 Communication Plan

Prior to the start of this study, the research team will complete the process for obtaining approval to recruit participants from UM DFM clinical sites, which includes obtaining permission from the UM DFM Associate Chair for Research (Dr. Caroline Richardson), as well as clinical site medical directors.

Any proposed changes to the study protocol which would change the role of the recruitment sites will be communicated via email to UM DFM Associate Chair for Research and the clinical site medical directors and agreed upon prior to seeking IRB approval.

UM DFM Associate Chair for Research and the relevant clinical site medical director will be informed via email once recruitment at each individual site has been closed.

10.0 References

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