

Protocol

1. Project Title

Trial of Preemptive Pharmacogenetics in Underserved Patients (TOPP UP)

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2. Investigators

Principal Investigator:

Julio Duarte, Pharm.D., Ph.D.
Assistant Professor
Department of Pharmacotherapy and Translational Research
UF College of Pharmacy

Co-Investigators:

Larisa Cavallari, Pharm.D.
Professor
Department of Pharmacotherapy and Translational Research
UF College of Pharmacy

Carla L. Fisher, Ph.D.
Professor
Department of Health Outcomes and Biomedical Informatics
College of Medicine

John Z. Malaty, M.D.
Associate Professor
Department of Community Health and Family Medicine
UF College of Medicine

Ross Jones, M.D.
Assistant Professor
Department of Community Health and Family Medicine
UF College of Medicine – Jacksonville

Grant Harrell, M.D.
Assistant Professor
Department of Community Health and Family Medicine
UF College of Medicine

Emily Cicali, Pharm.D.
Clinical Assistant Professor
Department of Pharmacotherapy and Translational Research
UF College of Pharmacy

3. Abstract

Little information exists regarding clinical implementation of pharmacogenetics (PGx) in medically underserved patient populations. Our preliminary data indicate that underserved patients are prescribed a higher rate of drugs with available PGx guidelines (PGx drugs). Thus, an important knowledge gap exists regarding the use of PGx in a patient population that may be the most likely to benefit clinically. The objective of this project is to determine the feasibility of low-cost, preemptive PGx testing in medically underserved patients, as well as its effect on patient medication satisfaction. To achieve this objective, we will complete a randomized open-label clinical trial comparing medically underserved patients receiving preemptive PGx testing to those receiving usual care. At completion of the proposed research, we expect to have developed valuable data identifying patients most likely to benefit from preemptive PGx testing and important effectiveness and feasibility data regarding its clinical implementation. These results should have a positive impact because they can inform future large preemptive PGx clinical trials assessing clinical outcomes as well as clinical implementation efforts, ideally reducing healthcare disparities in the field of precision medicine.

4. Background

For over 30 years, we have known that genetic polymorphisms affect patient response to many drugs. Despite this, the clinical use of pharmacogenetic (PGx) testing outside of cancer is still not widespread. Currently, clinical PGx testing is primarily limited to large academic medical centers, which excludes most patients in rural America who generally do not live near cities where these medical centers are located. In addition, with healthcare costs rising rapidly, there appears to be little appetite for additional reimbursements in our current fee-for-service healthcare model.[1] Thus, many health insurers often refuse to reimburse for many PGx tests, requiring patients to pay for the tests themselves. This practice excludes low-income patients who may be unable to incur the out-of-pocket expense. Lastly, many PGx tests have been developed using data primarily from subjects of Asian and European descent, reducing the clinical applicability of some tests in patients of Latino or African descent.[2]

Most experts in the PGx field agree that clinical implementation will eventually evolve to a preemptive testing model where patients are tested for multiple pharmacogenes at one time, with these data stored in their electronic health record (EHR) until needed.[3,4] Preemptive testing is more efficient because there is greater clinical utility when a patient's genotype is known before a medication is prescribed, reducing the risk of treatment failure or adverse effects. In addition, because there is no urgency for providing preemptive results, test batching in high volumes can dramatically decrease genotyping costs on a per-patient basis. Thus, the most feasible/sustainable way to facilitate future PGx clinical implementation will likely involve preemptive genotyping. However, due to the challenges described above, little is known about how to implement such a strategy in racial minorities, low-income patients, and other traditionally underserved populations.

5. Objectives and Aims

Objective. Our long-term goal is to contribute toward the efficient implementation of PGx into clinical practice to improve the precision of medication prescribing. The overall objective for this study is to identify PGx drug usage patterns in medically underserved patients and assess the feasibility and effectiveness of preemptive PGx testing in this patient population. The central hypothesis is that medically underserved patients are prescribed more PGx drugs, and preemptive PGx testing in this

population is feasible as well as effective in improving patient medication satisfaction. The rationale for the proposed research is that identifying patient populations that can most benefit from PGx testing will facilitate clinical implementation that may ultimately reduce disparities in medication-related outcomes.

Specific Aim. Determine the feasibility of low-cost preemptive PGx testing in a medically underserved population as well as its effect on patient medication satisfaction. Our working hypothesis is that preemptive PGx testing in medically underserved patients is feasible and will improve medication satisfaction compared to patients who receive usual care. We will test this hypothesis by completing a randomized open-label clinical trial comparing medically underserved patients receiving preemptive PGx testing and those receiving usual care. We will also assess key implementation metrics.

6. Research Plan:

Study Population and Setting. This study will include patients recruited from UF Health clinics that primarily serve medically underserved patient populations (**Table 1**). These clinics serve patients in rural, suburban, and urban areas.

Table 1. Subject Recruitment Clinic Sites

Clinic Name	*Location*	*Clinic Setting*
UF Health Family Medicine Main St.	Gainesville, FL	Suburban
UF Health Family Medicine Eastside	Gainesville, FL	Suburban
UF Health Family Medicine Old Town	Old Town, FL	Rural
UF Health Total Care Clinic	Jacksonville, FL	Urban
UF Health Family Medicine and Pediatrics-Elizabeth G. Means Center	Jacksonville, FL	Urban

Inclusion criteria are designed to identify patients who have common conditions that are more likely to benefit from PGx testing in the near future, while exclusion criteria are designed to eliminate scenarios that might confound the primary analyses.

Table 2. Previously Tested Pharmacogenes for Study Exclusion

ABCG2	DPYD
CYP2B6	NAT2
CYP2C19	NUDT15
CYP2C9	SLCO1B1
CYP2D6	TPMT
CYP3A4	UGT1A1
CYP3A5	VKORC1

<u>Inclusion Criteria:</u>

1. Adults (18 years or older) with active prescriptions for at least 3 medications documented within the EHR
2. Diagnosis of a condition that might be treated by a PGx drug (See Table 3).
3. An oral medication change within the past 8 months (associated with any healthcare provider encounter, regardless of the clinic.)

<u>Exclusion Criteria:</u>

1. Patients with prior clinical pharmacogenetic test results within the EHR for genes relevant for this study (Table 2).
2. Any medical condition that would prohibit the ability to complete study surveys
3. History of allogenic stem cell or liver transplant
4. History of chronic kidney dialysis
5. Life expectancy less than 12 months

Table 3. Diagnoses for Study Inclusion

Diagnosis	*Associated Drug or Drug Class*
Generalized depression	SSRI or TCA
Anxiety	SSRI
Inflammatory bowel disease	Azathioprine or mercaptopurine
Gastroesophageal reflux disease	PPI
Erosive esophagitis	PPI
Gastric ulcer	PPI
Acute coronary syndrome	Antiplatelet or beta-blocker or statin
Chronic pain	Opioid
Fibromyalgia	Opioid or NSAID
Rheumatoid Arthritis	NSAID
Osteoarthritis	Opioid or NSAID
Dyslipidemia	Statin
Heart failure	Beta-blocker
Deep vein thrombosis	Anticoagulant
Atrial fibrillation	Anticoagulant
Stroke	Antiplatelet

SSRI-selective serotonin reuptake inhibitor; PPI-proton pump inhibitor; NSAID-nonsteroidal anti-inflammatory drug

Participant Recruitment Methods. Patients with upcoming appointments at participating UF Health clinics will be screened for potential eligibility. The electronic health record will be reviewed to identify potentially eligible participants using the study inclusion/exclusion criteria. Clinic personnel at the corresponding participating clinic will be notified when a patient qualifies for the study and will be

asked to discuss the study with their patients. Patients can be recruited by study staff by the methods below:

1. Clinic providers or staff ask identified potentially eligible patients if they are interested in participating and they acknowledge that they are interested.

2. Clinic provider or staff will provide identified potentially eligible patients an approved advertisement (flyer) and the patient can directly contact study staff if interested.

3. Patients see IRB-approved advertisement and contact study staff directly to inquire about their eligibility.

4. The study team mails patients a recruitment letter notifying them that they may potentially be eligible to participate in the study. The recruitment letter will include instructions for how to opt out of the study and how to contact study staff if they are interested in participating. The recruitment letter will also inform the patient they may receive a phone call from the study staff about participating in the study.

Interested patients may be contacted in person while still in clinic, via mail, or via phone after their clinic visit if in-person contact is not possible. A research coordinator will review the consent document with the patient prior to enrollment. The consenting process can be in-person or remote through electronic means. Prospective research participants will have the opportunity to ask questions before providing consent and will be provided with a signed copy of the consent form after signing the form.

Study design. This will be a prospective, randomized, pragmatic, hybrid clinical trial assessing both the real-world effectiveness as well as implementation outcomes associated with clinical preemptive pharmacogenetic testing in medically underserved patients.

After providing informed consent, subjects will be randomized in a 1:1 allocation to receive either preemptive (immediate) PGx testing or usual care (delayed PGx testing) and will be followed over 12 months. Subjects in both assignment groups will provide a DNA sample (saliva, buccal swab, or blood) within 1 month of study enrollment**.** If the genotyping fails with initial sample collection, the patients may be mailed a DNA collection kit for saliva or buccal cell sample collection for retesting or asked to complete a blood draw. Patients in the delayed testing group can have samples re-collected at any time within the study period because their genotyping will not occur until the end of their study participation.

Table 4. Principal Study Outcomes

Outcome/Measure	Data source/Instrument	Baseline	6 mo.	12 mo.
Effectiveness Outcomes				
Treatment satisfaction	Treatment Satisfaction Questionnaire for Medication (TSQM)	X	X	X
Medication changes	EHR data	X		X
Provider encounters	EHR data	X		X
Medication adherence	PROMIS Adherence Questionnaire	X	X	X
Quality of life	HRQOL-4	X	X	X
Implementation Outcomes				
Perceived value	Patient reported value	X	X	X
Time discussing meds w/ healthcare provider	Patient reported estimate	X	X	X
Prescriber acceptance of automated alert recommendations	EHR data		X	X
Total intervention cost	EHR and Laboratory data		X	X

Questionnaire for Intervention participants	Patient report		X	X
Other Patient Measures				
Demographics	Patient report	X		
Socioeconomic factors	Patient report	X		
Medical literacy	Patient report	X		X
Willingness to pay	Patient report	X		X

Subjects assigned to the preemptive PGx group will be tested and have their results both entered into the EHR as well as provided to them (see Communication of genotype results below) within 1 month. Subjects assigned to usual care will not be tested until the end of their study participation, and their results will not be released until after their participation in the study has ended.

Upon study enrollment, and at 6 month and 12 month time points, subjects will complete surveys regarding their demographics, socioeconomic status, medical history, medication satisfaction, and their healthcare utilization use (**Table 4**). In addition to these measures, implementation-specific questions will be asked to assess the feasibility and sustainability of the intervention as well as assessments of intervention fidelity and adaptations. An approximately 1-month window will be permitted for each follow-up study interaction. In addition, data regarding medical encounters, medication prescribing, and documentation resulting from PGx testing will be collected from the patient's electronic health record (EHR).

Communication of genotype results: PGx testing will be completed using a newly-designed pharmacogenetic testing panel, which will be available for clinical use in the CAP/CLIA certified UF Molecular Pathology Laboratory. Once results are entered into the EHR, a clinical note, written by a UF Health Precision Medicine Program (PMP) pharmacist, will provide basic guidance on the most clinically impactful results for that patient. In addition, Clinical Decision Support Best Practice Advisories that are already built into Epic (and used clinically) will alert providers if a PGx interaction might occur with a medication they prescribe. All clinical medication decisions will be made at the discretion of the healthcare provider.

In addition to PGx results placed in the EHR, patients will be given, either via mail or in person, a laminated card containing their PGx results. This card will be approximately the size of a credit card and will be designed for them to show to any non-UF Health provider that they see. The card will be designed for a provider to read, and methods to obtain explanations and further information will be included on the card. A letter will be provided with the card explaining its intended use. Study staff will also follow up with a phone call or in person with patients to further explain the card and provide patients the opportunity to ask questions.

Effectiveness and implementation data collection: The primary effectiveness outcome will be change in patient treatment satisfaction between baseline and 12 months after PGx testing. This patient reported outcome will be measured via the TSQM. The TSQM is a validated tool that assesses three medication-related domains (effectiveness, side effects, and convenience) to synthesize a global satisfaction score.[7,8] Both global satisfaction and scores from individual domains will be analyzed.

An important secondary outcome assessing efficacy will include the number of medication changes within the 12-month follow-up period. Medication changes will be defined as the addition, removal, or dosage change to any PGx medication or medication within the same drug class. Comparisons of this outcome should estimate differences in trial-and-error drug dosing that is traditionally used in practice. Other secondary outcomes that will be analyzed include: The prescriber acceptance rate of PGx EHR alert recommendations, number of encounters with a healthcare provider over the study period, genotype turnaround time, and estimated time spent discussing medications with a healthcare provider. These outcomes will be used to assess feasibility.

Other Measures: We will assess whether socioeconomic factors influence testing feasibility and patient satisfaction to preemptive PGx testing. Patients will answer survey questions related to their education, employment, and income (**Table 4**). In addition, patients will answer questions regarding their medical literacy and their willingness to pay for clinical pharmacogenetic testing.

Qualitative data collection: An estimated sample size of 40 patients from the already recruited participants will be asked to complete an optional semi-structured interview assessing patient perspectives and desires for preemptive PGx testing and the communication of their results. Patient sampling will be aimed at achieving an approximately even distribution of sex and race.

Qualitative data collection will follow a sequential explanatory approach[9,10] to expand on findings from the quantitative analyses of patient survey data. Following the initial study visit, patients will be asked to provide additional consent for participation in an in-depth, semi-structured, audio-recorded phone or audio/video teleconference (e.g. Zoom) interview expected to take 20-30 minutes. They will receive additional compensation for participation. The interview will be conducted using a semi-structured script, with interviewers trained by a qualitative method expert. Interviews will explore patients' perspectives on implementation outcomes associated with the intervention to identify best practices in three key areas: 1) factors (barriers and facilitators) impacting willingness to undergo PGx testing; 2) preferences for the overall testing process (to identify strategies to improve upon intervention adoption and sustainability); and 3) preferences for the delivery of results, including best provider-patient communication approaches (and related challenges) as well as practices for sharing results (e.g., with other providers or family). Thematic findings have emerged in samples of 15-20 participants.[11,12] An estimated sample of 40 participants will be recruited, but recruitment will end once thematic saturation has been attained. Data analysis of transcribed interviews and data collection will be concurrent to ensure thematic saturation can be met.[13]

Sample Size Determination: Trial sample size was calculated based on the primary effectiveness outcome, global TSQM score. To detect a 10% (7.1 points) difference in scores (SD = 22.6 points) between the genotype and control groups with 90% power and an alpha of 0.05, we would need 214 subjects in each group. Due to the relatively long follow-up period (1 year), we anticipate up to a 21% attrition rate. Thus, we estimate that we will need to recruit 542 subjects to successfully complete the study.

Subject Compensation: Subjects will receive compensation for the time required for questionnaire completion. They will receive $25 in the form of a pre-paid US Bank Gift card and/or a digital payment through Zelle, upon completion of the baseline survey, another $25 upon completion of the 6-month survey, and another $25 upon completion of the 12-month survey. Subjects who complete a semi-structured interview will receive another $40 upon interview completion.

Analysis plan: Differences in TSQM and other continuous variables described above will be initially compared between genotype and control groups using Student's t-test or Mann-Whitney U test, depending on the data distribution. In addition to univariate analyses, multiple regression models will also be completed for each outcome, adjusted for potential covariates, such as age, race, sex, study site, and Charlson Comorbidity Index. Subgroup analyses (e.g. by sex, race, age groups) will also be conducted to assess the role of potential biological variability in subject response. In all analyses, a two-sided $P \leq 0.05$ will be considered statistically significant, and all statistical analyses will be completed in R version 4.0.1.

Possible Discomforts and Risks:

Risks involved with participating in this study are minimal, and are described below.

Accidental disclosure of PHI:
To safeguard against this, electronic data will be stored in a custom-designed REDCap database, which is encrypted and password-protected. Paper documents and other physical media will be stored in a locked cabinet within the PI's locked, private office or the secure Precision Medicine Program research office.

Blood Draw:
The risks of a blood draw include pain, bruising, and the slight possibility of infection at the location of needle insertion. Some participants may feel dizzy or may faint during or after a blood draw.

Genetic Discrimination:
While the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against participants based on their genetic information, federal law does not protect patients against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. The pharmacogenetics examples included in our study are only known to be associated with drug response, which is unlikely to lead to insurance discrimination as long as effective, alternative therapies are available, as they are for all gene-drug pairs included in this study.

Due to the nature of the study, adverse events are not anticipated. However, if any events are observed, they will be reported to the IRB in a manner consistent with UF regulations.

8. Possible Benefits:

Subjects may not directly benefit from participating in this study. There is a possibility of direct benefit to individual subjects, as genotype information could lead to more effective drug prescribing. Nevertheless, in the absence of a direct benefit, the study may advance the field by providing an increased understanding of the utility and feasibility of preemptive PGx testing in traditionally underserved patient populations. Such understanding is deemed essential for broader dissemination of PGx into clinical care.

9. Conflict of Interest:

The investigators have no conflicts of interest to report. Publications that may result from such research could enhance the reputation of the investigators but are not expected to affect the conduct of this research.

10. References:

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