Protocol

1. Project Title: Clinical implementation pilot of preemptive pharmacogenetic testing in medically underserved patient populations

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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 associated with 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 clinically benefit. The objective of this project is to develop key feasibility data to equitably advance preemptive PGx testing within University of Florida Health, and to generate important preliminary data to support future larger

studies. We plan to accomplish this objective by pursuing three specific aims: (1) assess the feasibility of preemptive PGx clinical implementation in primary care clinics predominantly serving medically underserved patients; (2) understand perspectives about preemptive PGx among key stakeholders in the primary care clinics predominantly serving medically underserved patients; and (3) identify specific socioeconomic characteristics most strongly associated with PGx drug prescription rate. To achieve these aims, we will recruit patients for preemptive PGx testing from primary care clinics that primarily serve our target patient population, and use patient-reported outcomes, feedback from semi-structured interviews, and data collected from the electronic health record to assess testing feasibility and pilot outcome data. Upon successful completion of this project, we expect to have generated important preliminary data that can be used to support wider implementation of PGx testing to underserved patients and a variety of current and larger studies designed to further examine implementation of precision medicine technologies. This line of research will positively impact drug-related outcomes by reducing healthcare disparities in the field of precision medicine.

4. Background:

While, for over 30 years, we have known that genetic polymorphisms affect drug response, clinical use of pharmacogenetic (PGx) testing outside of cancer is still not widespread. PGx testing is primarily limited to large academic medical centers, which greatly limits the number of patients who have access to this technology and precision of drug therapy that it allows. 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 PGx tests, especially those done preemptively, requiring the patients to self-pay. This practice excludes low-income patients who are unable or unwilling to incur the out-of-pocket costs. Lastly, many PGx tests have been developed using data primarily from subjects of European descent, making their results less clinically useful for patients of Latino or African descent.

Current implementation patterns of PGx testing, as with other innovative technologies, have the potential to increase disparities in health care quality and outcomes, especially if there is greater preexisting need in the populations unable to access them. This phenomenon, known as the Inverse Equity Hypothesis,[2] will continue to occur unless specific access barriers are overcome when a new technology is implemented.

PGx testing may be particularly beneficial in medically underserved populations by reducing the number of medical encounters required to optimize drug therapy and preserving use of less expensive off-patent drugs – the type drugs most often with PGx guidelines available – for patients predicted to benefit based on their genotype results. This is supported by preliminary data from the University of Florida (UF) Health, which indicate that patients with poor geographic access to healthcare providers are prescribed a higher rate of drugs with PGx guidelines available (PGx drugs). Race compounds this disparity, with underserved black patients having both significantly fewer encounters with healthcare providers and more PGx drug prescriptions than underserved non-black patients. Because medically underserved patients use more PGx medications and visit their provider less often, these patients should benefit the most from preemptive PGx testing, where trial-and-error drug selection could be minimized. Thus, there is a critical need to gather data to inform clinical implementation of PGx testing in medically underserved populations to improve healthcare quality and assure equitable distribution of innovative healthcare technologies.

Most experts agree that clinical PGx implementation will eventually evolve to a preemptive testing model where patients are tested for multiple PGx variants at one time, with these data stored in their electronic health record (EHR) to inform future prescribing.[3,4] Pre-emptive testing is more efficient than “reactive” testing (i.e. at the time of drug prescribing) because most PGx tests have the most clinical benefit when genotype is known ***before*** a medication is administered, reducing the risk of treatment failure or adverse

effects. In addition, preemptive testing allows genotyping samples from many patients to be batched and run in high volume, which substantially decreases the genotyping cost per patient. Thus, the most feasible/sustainable way to facilitate the clinical implementation of PGx in underserved patients will likely involve preemptive genotyping.

To our knowledge, there have been no studies reporting implementation data of preemptive PGx testing in medically underserved patients. Further, there are few data in the literature regarding the perceptions and attitudes of black and Latino patients toward preemptive PGx testing. This work is significant because it is expected to contribute valuable data toward both the feasibility of preemptive PGx testing in medically underserved patients, an area of PGx research where little information is available. We anticipate these data will inform future multi-site clinical trials of preemptive PGx implementation.

5. Specific Aims:

Motivated by the critical need to expand access of preemptive PGx testing to underserved populations, the overall objective for this application is to develop key feasibility data to equitably advance preemptive PGx testing within UF Health, and to generate important preliminary data to support future funding applications. The rationale for this project is that generating these feasibility data should facilitate equitable clinical implementation that may reduce medication treatment disparities, as well as inform future larger clinical studies. We plan to accomplish the overall objective of this application by pursuing three specific aims:

1. Assess the feasibility of preemptive PGx clinical implementation in primary care clinics predominantly serving medically underserved patients. We will provide clinical preemptive PGx testing for 100 patients from specific UF Health clinics serving mostly medically underserved patients, including clinics with a high rate of black and Latino patients. We will assess feasibility of this implementation effort by comparing patient-reported outcomes data abstracted from electronic health records before and 6 months after PGx testing.

2. Understand perspectives on preemptive PGx testing among key stakeholders in the primary care clinics predominantly serving medically underserved patients. We will conduct in-depth, semi-structured interviews with a subsample of recruited patients from Aim 1 and clinicians within the clinic sites to identify influential factors critical to implementing PGx testing, including motivations, barriers, and best practices for the delivery of results.

3. Identify specific socioeconomic characteristics most strongly associated with PGx drug prescription rates. Our preliminary data using EHR data from UF Health show strong correlations between zip code-derived healthcare geographic access scores and rate of PGx drug prescriptions. We aim to use the results of a validated socioeconomic estimation tool as well as individual measures of socioeconomic status in a single predictive model to determine which social determinants most associate with PGx drug prescription rate within the 100 patients from Aim 1.

6. Research Plan:

Study population and setting. This study will include UF Health patients recruited from clinics that serve mostly medically underserved areas. Primarily, this will include the UF Health Family Medicine Eastside and Main St. Clinics, which serve a large number of low-income, black and Latino patients. Overall, we plan to recruit 100 patients from targeted clinics. Inclusion criteria are designed to identify patients who have a high possibility of benefitting from PGx testing.

Inclusion Criteria:

1. Adults (18 years or older) with active prescriptions for at least 3 medications documented within the EHR.
2. At least 1 drug/drug class that could be informed by the PGx test panel (See Appendix A for complete list).
3. A medication change within the past 6 months (associated with a healthcare provider encounter)
4. Self-identify as black or Latino.

Exclusion Criteria:

1. Patients with any history of PGx testing within the EHR.

Participant Recruitment Methods.

Patients may be approached for the study in various way including clinic intercepts, study flyers and clinic referrals. The electronic health record will be queried to identify potentially eligible participants using the inclusion/exclusion criteria. Providers (including but not limited to physicians, nurse practitioners, and pharmacists) who care for patients at UF Health will be notified when their patients qualify for the study and will be asked to discuss the study with their patients.

Patients can be recruited by study staff via two methods:

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

2. Clinic provider or staff will provide patients an approved flyer and they contact study staff if interested.

If recruitment occurs during a clinic visit, patients meeting eligibility criteria will be approached by a research coordinator about study participation. Patients may also be contacted via phone after their clinic visit if in-person contact is not possible (for example, but not limited to, space limitations due to COVID-19 restrictions).

A research coordinator will review the consent document with the patient prior to enrollment. The consenting process can be in-person or remote via telephone or 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 providing written informed consent, a DNA sample will be collected from all patients by saliva (via mouthwash swish and expectorate collection) or buccal cell (via buccal brush/swab). 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.

Study design. After eligible participants provide written informed consent and are enrolled, a DNA sample will be obtained for PGx testing and questionnaires (as described below) will be administered at baseline, and then again at 3 months and 6 months after PGx results are entered into the EHR. Information will be abstracted from the EHR including PGx test results, medication changes, and healthcare provider encounters over the 6-month study duration (Table 1). A 1-month window will be permitted for each follow-up study interaction (± 15 days of exact due date).

PGx testing will be completed using the GatorPGx panel, which is already available for clinical use in the CAP/CLIA certified UF Molecular Pathology Laboratory. Once results are entered into the EHR, Clinical Decision Support Best Practice Advisories already built into Epic 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.

Table 1. Proposed outcomes/measures to be tested

Outcome/Measure	Data source/Instrument	Ascertainment method	Baseline	3 mo.	6 mo.
Implementation Outcomes					
Treatment satisfaction	Treatment Satisfaction Questionnaire for Medication (TSQM)	Online or by phone	X	X	X
Medication adherence	Adherence Questionnaire	Online or by phone	X	X	X
Perceived value	Patient reported value	Online or by phone	X	X	X
Time discussing meds w/ healthcare provider	Patient reported estimate	Online or by phone	X	X	X
Effectiveness Outcomes					
Medication changes	EHR data	EHR data pull	X		X
Provider encounters	EHR data	EHR data pull	X		X
Socioeconomic Measures					
SEI	Patient report	Online or by phone	X		
Occupation	Patient report	Online or by phone	X		
Education level	Patient report	Online or by phone	X		
Household Income	Patient report	Online or by phone	X		
Household zip code	Patient report	Online or by phone	X		

Feasibility data collection: The primary feasibility outcome will be change in patient treatment satisfaction between baseline and 6 months after PGx testing. This patient reported outcome will be measured via the Treatment Satisfaction Questionnaire for Medication (TSQM). The TSQM is a validated tool that assesses three medication-related domains (effectiveness, side effects, and convenience) to synthesize a global satisfaction score.[5,6] 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 6-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. These outcomes are important because if the results suggest that preemptive PGx testing is associated with increased patient treatment satisfaction, a reduction in medication changes, or increased perceived value of PGx testing, these findings would support expanded clinical implementation in medically underserved patients. This might also suggest that PGx could be further used as a tool to minimize disparities in pharmacotherapy. 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 and will inform design of a large clinical trial to be funded by future grants.

Socioeconomic data collection: We have previously observed significant associations between calculated geographic access scores and rate of PGx drug prescriptions, which considerably strengthened in subanalyses by race. Whether this association is exclusively related to geography and race or whether it is also related to socioeconomic determinants is unknown. Thus, we will test whether socioeconomic status is a social determinant of health related to PGx drug usage. Patients will answer survey questions related to their education, employment, and income (Table 1).

Qualitative data collection: An estimated sample size of 20 patients from the 100 recruited participants will be recruited for this aim. Patient sampling will be aimed at achieving an approximately even distribution of sex (male and female) and race (Latino and black).

Qualitative data collection will follow a sequential explanatory approach[8,9] to expand on findings from the quantitative analyses of patient survey data in Aim 1. Following the initial study visit, patients will be asked to provide additional consent for participation in an in-depth, semi-structured, audio-recorded phone interview expected to take 20-30 minutes. They will receive additional compensation for participation. A semi-structured script will be developed 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.[10,11] An estimated sample of 20 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.[12]

Subject Compensation: Subjects will receive compensation for the time required for questionnaire completion. They will receive $20 (cash or gift card) upon completion of the baseline survey and another $20 upon completion of the 6-month survey. Subjects who complete a semi-structured interview will receive another $20 upon interview completion.

Analysis plan. For Aim 1, implementation outcomes such as prescriber acceptance, turnaround time, and cost will be assessed using descriptive statistics. Differences in patient reported outcomes such as treatment satisfaction, perceived value, and effectiveness outcomes (Table 1) will be initially compared between baseline and 6 months 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, clinic site, and Charlson Comorbidity Index. In all analyses, a two-sided $P \leq 0.05$ will be considered statistically significant, and all statistical analyses will be completed in R ver. 3.6.3.

For Aim 2, interview transcripts will be managed using data management software (e.g., Nvivo or Atlas.ti). Data will be thematically analyzed using the widely used constant comparative method.[13] This systematic approach involves several coding steps including identifying concepts and assigning codes, 2) grouping categories of emergent themes, and 3) axial coding to identify thematic properties. To ensure similarities and differences between patients' experiences can be captured, data analysis will be segmented by group and triangulated with survey data collected from healthcare providers (via separate protocol). Triangulation of data between sources also enhances the validity of the findings.[14] Multiple coders, trained in the CCM approach, will conduct the analysis to ensure rigor. Meetings will be held to compare independent coding, discuss differences in interpretation, collapses analyses, and continuously refine the codebooks. Codebooks will be developed with each stakeholder group dataset. Once codebooks are finalized and analyses complete, each analysis will be validated by an additional coder analyzing a subset of the transcripts from each group.[12] Operational and thematic memos will be maintained across data collection and analysis to ensure researcher reflexivity, thematic saturation, and rich description of themes.

For Aim 3, total scores and scores within individual domains will be compared with number of medications prescribed, number of healthcare encounters, and PGx drug prescription rate. Comparisons will be completed in univariate analyses via Spearman's correlation test. In addition, multiple regression models will be developed to allow the ability to adjust for potential confounders such as age, and Charlston Comorbidity index. In addition, we will estimate the proportion of variation in PGx prescription rate that can be explained by each socioeconomic measure by comparing coefficients of determination (r^2) in each model.

7. Possible Discomforts and Risks:

Risks involved with participating in this study are minimal, and include 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. 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 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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Appendix A: List of medications that could potentially be informed by preemptive pharmacogenetic (GatorPGx) panel

Medication	Gene
Selected SSRIs (escitalopram, citalopram, sertraline)	*CYP2C19*
PPIs (pantoprazole, dexlansoprazole esomeprazole, lansoprazole, omeprazole)	*CYP2C19*
Clopidogrel	*CYP2C19*
Voriconazole	*CYP2C19*
High dose TCAs (amitriptyline, nortriptyline, clomipramine, doxepin)	*CYP2C19, CYP2D6*
Certain opioids (codeine, tramadol, hydrocodone, oxycodone)	*CYP2D6*
Certain SSRIs (paroxetine, fluvoxamine)	*CYP2D6*
Ondansetron	*CYP2D6*
Atomoxetine	*CYP2D6*
Tamoxifen	*CYP2D6*
Phenytoin	*CYP2C9*
Warfarin	*CYP2C9, VKORC1, CYP4F2*
Selected NSAIDs (celecoxib, ibuprofen, meloxicam, flurbiprofen, lornoxicam, piroxicam, tenoxicam)	*CYP2C9*
Tacrolimus	*CYP3A5*
Simvastatin	*SLCO1B1*
Thiopurines (azathioprine, mercaptopurine, thioguanine)	*TPMT*