PHARMACOGENETIC TESTING IN A COMMUNITY PHARMACY SETTING

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INTRODUCTION

Background

Pharmacogenetic (PGx) testing may inform drug dosing or selection through knowledge of a patient's likelihood to respond to a drug or risk of an adverse drug response (ADR).[1] Genetic variation has been estimated to account for 20-95% of individual responses to medications.[2] Up to 80% of drugs are believed to be metabolized by one of three polymorphic cytochrome-P450 (CYP) genes: *CYP2D6, CYP2C19, and CYP2C9*.[3] Phillips et al.[4] identified 27 drugs with frequently reported ADRs, 59% of which are metabolized by at least one CYP enzyme. Given the substantial health care costs associated with ADRs,[5,6] and increasing use of prescription drugs in the U.S.,[7] efforts to reduce the prevalence of ADRs and improve drug selection may help reduce costs, improve timely treatment, and lead to additional benefits such as increased medication adherence.

As with most medical innovations, the uptake and integration for PGx testing are impacted by several factors including provider knowledge, clinical evidence, patient interest, and reimbursement.[8] From our previous research, we have learned that most physicians have little knowledge of what PGx tests were available and for which drugs, the purpose of testing, and applicability of test results,[9] (findings confirmed by other groups.[10,11]) Although some PGx tests have been taken up relatively rapidly in clinical practice,[12] others have had limited or delayed uptake.[13] In addition to limited knowledge about PGx testing, some providers may have very limited time during an office visit to discuss PGx testing.[14]

The pharmacy practice has greatly evolved, expanding from traditional roles of compounding and dispensation to provision of a range of clinical services including vaccinations, clinical testing (e.g., cholesterol, A1C, and glucose), and medication therapy management (MTM).[15,16] With an estimated 55,000 community pharmacies in the U.S., these settings enable more convenient access to health services that were once limited to physicians' office[17]. It is estimated that 56% of all prescriptions are filled at chain pharmacies, 15% at independent pharmacies, and 20% through mail order.[18] Several studies have demonstrated that pharmacists' direct involvement in patient care can reduce health costs and improve clinical outcomes[19-21] and they are a trusted resource by patients[22,23] While pharmacists have been involved in implementation of PGx testing in clinic-based or hospital settings, often as a liaison between the testing laboratory and provider,[24-26] the feasibility and impact of community pharmacist-delivered PGx testing has not been explored in depth.[35,43]

One delivery option that has not been explored in-depth is providing PGx testing through the community pharmacy. As pharmacists have expertise about drugs and regularly interact with both patients and providers, they occupy a unique position in the health care delivery team and may be ideally suited to provide PGx testing. Patients often rely on their community pharmacist not only to dispense medications, but as a source of medical information and for other health services (e.g., vaccinations)[27]. Some commercial laboratories have begun to establish partnerships with community pharmacies to offer PGx testing, but to our knowledge, no studies have been conducted about pharmacists' preparedness, interest, utility, or patient experiences with PGx testing in this setting.

To address patient needs and maximize outcomes of PGx testing, it has been proposed to deliver PGx testing as part of MTM.[28,29] MTM services have transitioned from primarily patient education and counseling to systematic and coordinated processes for comprehensive medication

management.[30] MTM is currently being utilized in community pharmacies and ambulatory care settings as a standard of care to address adherence, side effects, duplication of therapies, and prevention of possible drug interactions. Though practices can vary,[31] MTM services typically include five core elements: 1) medication therapy review, 2) personal medication record, 3) medication-related action plan (MAP), 4) intervention and/or referral, and 5) documentation and follow-up.[32] Typically conducted by a pharmacist, MTM can be helpful for physicians and patients to improve medication adherence. MTM has been shown to be effective for some patient populations in reaching clinical goals, increasing compliance with recommended lab monitoring, reducing re-hospitalizations and inappropriate prescribing and risk of ADRs, and improving adherence.[20,33-39] For a range of clinical goals, MTM has also been demonstrated to be cost-effective.[35,40,41]

This service is currently being supported by CMS for Medicare Part D programs, which give patients the opportunities address medication concerns and lead them to better outcomes with their medication use (https://www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovcontra/mtm.html). Furthermore, many independent insurance plans and employers have integrated MTM therapy options for their patrons that have many comorbid conditions. If modifications to a patient's current drug regimen are warranted, the pharmacist serves as a liaison between the prescriber and patient. When a pharmacist identifies issues with a patient's prescription regimen (i.e. duplicate treatments, contraindicated prescriptions, etc) he or she will contact the prescribing physician and make recommendations for changes to the patient's treatment regimen. This same approach is feasible with the integration of PGx: the pharmacist can contact the provider about the patient's PGx results and how it and other factors impact the patient's current regimen. The provider would have the PGx results on hand as they are faxed to the prescribing provider from both the lab and the pharmacy. Therefore, the pharmacist would present the patient's PGx results and recommendations to the provider, and the provider would adjust the medication at their discretion.

Significance

We propose to explore the effect of two delivery models through the community pharmacy setting for PGx testing. Demonstration of effective delivery models for PGx testing will be essential to promoting more routine and widespread use in clinical practice. In most delivery models currently utilized, testing is ordered by the treating provider at the time of treatment or preemptively (e.g., upon hospital admission).[42] The delivery of PGx testing through the community pharmacy may overcome challenges currently faced by physicians (e.g., time and knowledge), facilitating the appropriate use of PGx testing and serving as an educational and expert resource for patients and providers, respectively.

The provision of PGx testing is a logical extension of services provided at the community pharmacy for several reasons. **First,** pharmacists have experience with clinical testing and have expressed an interest in personalized medicine and PGx testing.[43-45] In addition, pharmacists are interested in providing MTM services[46] as evidenced by the increasing number of MTM providers,[47] and development of new partnerships[48,49] and business strategies.[50,51] **Second,** patients are interested in PGx testing, particularly those that have experienced ADRs[52] and appear to be receptive of new services offered by community pharmacists, including MTM.[53] For example, one study reported that more than half (52%) of the patients completed the home fecal

immunochemical test, demonstrating acceptance of a lab test offered by pharmacists.[54] Similarly, a pilot study of PGx testing offered as a stand-alone service in a single community pharmacy reported 43% uptake.[55] We surveyed community pharmacies offering PGx testing and found patient uptake to be relatively high (81%). **Third,** physicians' acceptance of pharmacist recommendations suggests that pharmacists can help prescribers apply PGx results to decisions regarding dosing or selection, reducing the burden on physicians[55,56]. **Therefore, pharmacists' expert knowledge of drugs, patient and pharmacist interest in PGx testing and MTM, and physician acceptance of pharmacists' recommendations combine to support an optimal delivery model of PGx testing in the community pharmacy setting.**

The inclusion of PGx testing specifically in MTM services may have many advantages. Pharmacists are uniquely trained to understand the underlying biology of PGx , i.e., pharmacology, drug metabolizing enzymes and transporters, etc. In addition, pharmacists are trained to provide patient counseling[57] and thus, could provide the patient education necessary given patients' likely unfamiliarity with PGx testing.[52,57] A review of a patient's medication history may identify multiple drugs impacted by a PGx variant in addition to the drug for which testing was indicated. Pharmacists can communicate with prescribers regarding recommended medication changes based on the test results, filling a gap in prescriber knowledge about PGx testing and interpretation of results. Lastly, policies are changing to enable greater access/ enrollment to MTM services. In 2011, the MTM Empowerment Act was passed, further expanding MTM coverage under Medicare Part D. Pharmacists can bill directly for MTM services with established CPT codes for initial, follow-up, and additional sessions in 15 minute increments. Professional organizations are advocating for federal policies regarding provider status and expanded support for MTM. Collaborations between pharmacists and providers can enable broader delivery of MTM services[58] and improve star ratings.[59,60]

However, pharmacist implementation of MTM may face some barriers.[61,62] Challenges to the provision of PGx testing as part of MTM can be divided into two general areas: 1) education/preparedness and 2) feasibility.[63-66] Pharmacists have recognized their limited knowledge of PGx.[43-45,65] Many professional groups have recommended enhanced training in PGx for pharmacists,[67-71] and several formal and continuing education (CE) training programs have been developed.[72,73] To address some of these issues, we have developed a suite of educational resources for the pharmacist and patient. In addition, the time required to perform MTM and reimbursement streams may pose barriers for busy community pharmacies.

PURPOSE

Given the lack of evidence regarding the feasibility of various approaches to deliver PGx testing, this study will explore patient interest and the feasibility of pharmacist-delivered PGx testing in a community pharmacy setting. Specifically, we will compare two pharmacist delivery strategies: a stand-alone PGx test or PGx testing with medication therapy management (MTM). Given the relative novelty of clinical testing in a community pharmacy for many patients as well as the anticipated unfamiliarity with PGx testing, we aim to assess patients' acceptance rates and perceived value, satisfaction, and comprehension of test result as well pharmacist factors that may impact feasibility of delivery in this setting. To our knowledge, this is the first study of its kind to compare delivery models of PGx testing in a community pharmacy setting. Pharmacies offer a promising alternative delivery location and our examination of their effectiveness will

advance knowledge in an important way.

STUDY OBJECTIVES

Aim 1. To finalize pharmacist and patient educational toolkits to facilitate delivery and communication of PGx testing in the community pharmacy setting and assess its utility. A 'toolkit' of pharmacist materials and patient handouts will be provided to each participating pharmacist to adequately deliver PGx testing alone or as part of an MTM service to patients in this study. We have developed multiple educational materials and tools for both pharmacists and patients to facilitate communication and promote patient comprehension, respectively. Prior to dissemination, we propose to gather additional feedback on these educational resources for use in the community pharmacy setting. We will solicit feedback from community pharmacists and patients to evaluate the educational toolkit components through semi-structured interviews. This part of the project has been submitted as a separate IRB protocol (#Pro00069061).

Aim 2. To compare the effect of PGx testing offered as a stand-alone or as part of medication therapy management (MTM) with respect to patient, pharmacist, pharmacy setting variables. Using a cluster randomized study design, pharmacies will be randomized to provide PGx testing only or PGx testing with MTM. Study outcomes will be gathered through pharmacist and patient surveys and follow-up interviews with pharmacists. The primary goal of the clinical trial is to study the difference between the effects of these two services on patient acceptance, comprehension, satisfaction, and medication adherence; secondary outcomes include acceptance of recommendations for drug/dosing changes (AIM 2a). The second part of this aim will evaluate pharmacist and pharmacy variables relevant to the sustainability of these delivery models (AIM 2b).

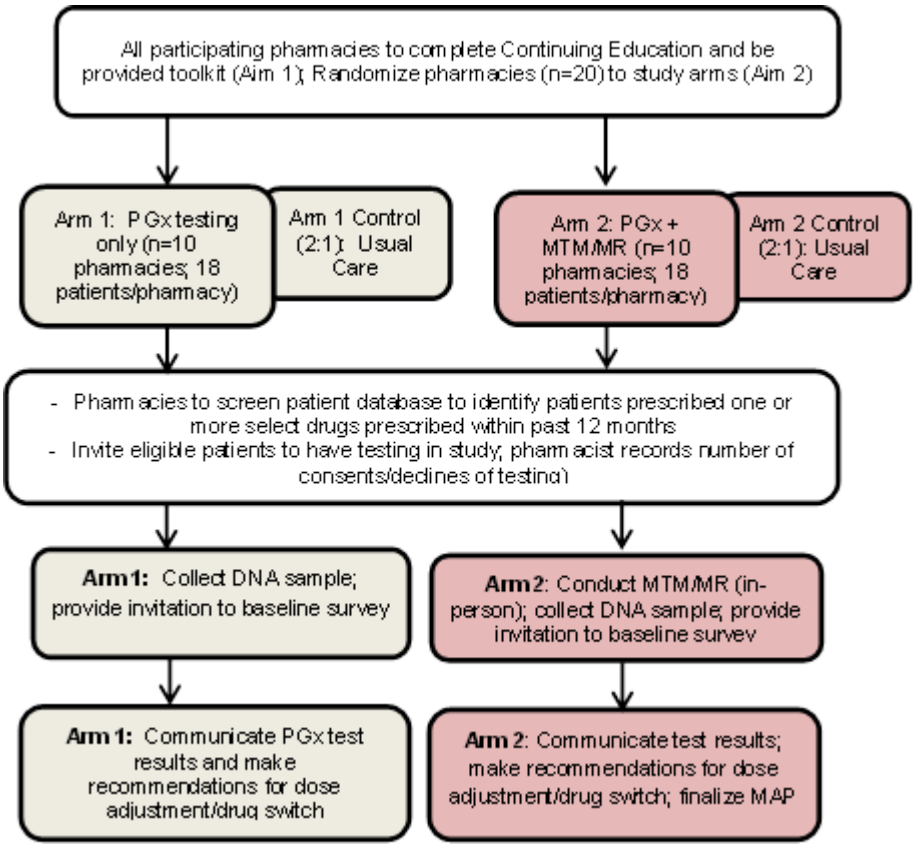
- 2a) Patient perceptions are increasingly used to assess quality of care. We will compare and assess patients' 1) satisfaction with testing experience in a pharmacy setting and perceived value of testing; 2) comprehension of test result; and 3) medication changes and adherence. We will collect demographic information that may be associated with patients' satisfaction, comprehension and perceived value of PGx testing, such as age and education status as well as information about past experiences with prescribed medications. Data will be collected through a baseline and one follow-up survey. We hypothesize that patients overall will be satisfied with PGx testing provided through the community pharmacy, particularly those who have experienced adverse responses or a poor outcomes, are taking multiple medications, and are older. Furthermore, we hypothesize that patients' increased awareness about their genetic risk to adverse responses will result in improved medication adherence and sharing of results with other providers. Patients with lower education status, chronic illnesses, and who are older may report greater benefit from PGx testing delivered as part of an MTM, with respect to comprehension and overall satisfaction. We will also assess whether patients' perceived value or satisfaction was influenced by the presence/absence of PGx variants.
- 2b) We will assess pharmacists' knowledge and experiences with delivery of PGx testing and determine the effort required to provide PGx testing with or without MTM and potential barriers to continuing this service, such as impact on other pharmacy services. A pre- and post-study survey will be developed and administered to participating pharmacists. The goal of the pre-

study survey will be to establish a baseline knowledge of and prior experience with PGx testing, patient education, and MTM services. For each patient tested, pharmacists will be asked to record 1) the time required to consent and discuss PGx testing (and conduct MTM for that study arm); 2) the time required to discuss results and significance of test results on treatment; and 3) time required to consult with prescribing prescriber if medication changes are indicated based on test result. The goal of the post-study survey will be to re-assess knowledge of and ease of offering PGx testing, perceived barriers to implementation, and likelihood to overcome these barriers and add PGx testing to current panel of pharmacy services. We anticipate that the additional time required to deliver PGx testing as part of an MTM session may present a barrier to providing PGx testing through this approach. However, patients may benefit more with respect to increased comprehension and satisfaction than those receiving testing as a stand-alone service and this may present a novel innovation that could be made available to patients.

INVESTIGATIONAL PLAN

Overview. We will conduct a cluster randomized trial to compare the effect of PGx testing as a stand-alone to PGx testing with MTM (Figure 1). A cluster randomized trial design is often used to assess health interventions, whereby *groups* of individuals are randomized, in contrast to traditional clinical trials that randomize individuals to study arms.[74] Community pharmacies will be randomized to provide PGx testing only or PGx testing with MTM. Outcome measures will include patient comprehension, acceptance, and satisfaction, impact on medication adherence, and drug or dosing adjustments. A 2:1 matched pharmacy population will be used as control arm. Study outcomes will be gathered through pharmacist and patient surveys and follow-up interviews with pharmacists. We anticipate the study period will last for 6-12 months, depending on the enrollment rate.

Figure 1. Overview of study (MTM= medication therapy management; MAP = medication action protocol; MR = medication reconciliation; PGx = pharmacogenetic).



PART I. PHARMACOGENETICS EDUCATIONAL MATERIALS & TRAINING

An important factor of translation of PGx tests is provider knowledge. All participating pharmacists in the study will be required to complete one or two training sessions: 1) an in-person continuing education session on PGx, overview of the study and the educational resources we have developed to facilitate the delivery of PGx testing in the community pharmacy setting; and 2) for pharmacists randomized to the MTM+PGx arm, an in-person MTM session to review elements of MTM, development of medication action plans, and incorporation of PGx testing into an MTM session. We have developed an educational "toolkit" comprised of 4 components to inform patients of PGx testing and their results by supplementing pharmacist discussions with patients. These components have been reviewed by pharmacists (Pro00062612) and updated according to their recommendations. We will conduct interviews with pharmacists and patients to provide additional feedback on the revised version of the toolkit (Aim 1). The toolkit will then be finalized and provided to participating pharmacists for use during the randomized trial (Aim 2)

A. Overview of Toolkit

The toolkit is comprised of four components to facilitate patient-pharmacist communication and patient comprehension in both pre-testing and post-testing phases (Appendix 1). The toolkit or certain components may be used by the pharmacist or provided to patients based on the pharmacist's preferences (suggested use of each tool will be described in the study overview presentation). The components of the toolkit have been used in the parent R01 and other pilot studies. We will finalize the toolkit components based on comments from both pharmacists and patients (see IRB #Pro00069061).

- A list of online resources will provided from the CPPN web-site (www.rxpgx.com), including PharmGenEd™ CME Modules;[72,73] the Pharmacogenomics Research Network,[75] the Washington University Medical Center warfarin dosing website,[76] and the FDA table of drug labels.[77] (Appendix 2)
- A test information sheet (TIS; Toolkit component #1) and results summary handout (Toolkit component #3) to help pharmacists discuss PGx testing with patients.[14] The TIS highlights key information about PGx testing to disclose to patients and was adapted from a patient brochure developed and informed by patient feedback and therefore, may also be used as patient handouts (Appendix 1).
- An illustrated flipbook (Toolkit component #2) to be used to introduce PGx testing to patients. A version of the flipbook was used in the community pharmacy study and will be further modified based on comments from pharmacists in that study as well as a survey of registered pharmacists in NC (Appendix 1). The flipbook is similar to those used by genetic counselors (e.g., spiral-bound board-type book of about 5 pages of pictorials) and is intended to aid the pharmacist to discuss the following concepts: 1) contrast "traditional" approach of prescribing medications to "personalized" prescribing based on the patient's genetic make-up; 2) a figure depicting how people metabolize drugs at different rates; and 3) a list of the genes for which testing will be available in the study and the prescribed drugs associated with them.[14]
- A patient results wallet card (Toolkit component #4) to record the patient's test results and

given to the patient (Appendix 1). The pharmacist will need to fill in the results for each patient; printed copies of the card on glossy heavy stock paper will be provided.

We will also provide some other resources to facilitate pharmacist delivery of PGx testing:

- A list of additional pharmacist resources including web-sites such as PharmGenEd™ CME Modules (Module I: Pharmacogenomic Principles and Concepts (http://pharmacogenomics.ucsd.edu/cpecme/module-i-pharmacogenomic-principles-and-concepts.aspx); Module II: Clinical Applications of Pharmacogenomics (http://pharmacogenomics.ucsd.edu/cpecme/module-ii-clinical-applications-of-pharmacogenomics.aspx), the Pharmacogenomics Research Network (http://www.nigms.nih.gove/Initiatives/PGRN), and the Barnes-Jewish Hospital at Washington University Medical Center warfarin dosing website (http://www.warfarindosing.org/Source/Home.aspx).
- Regular updates from the study pharmacist (accessible throughout the study) via email about new emerging issues, guidelines or discoveries in PGx.
- A poster to display in pharmacists' work area that includes general information about PGx testing, eligible drugs (Table 1), and contact information for the testing laboratory, study pharmacist, and study coordinator.

B. Pharmacist Continuing Education

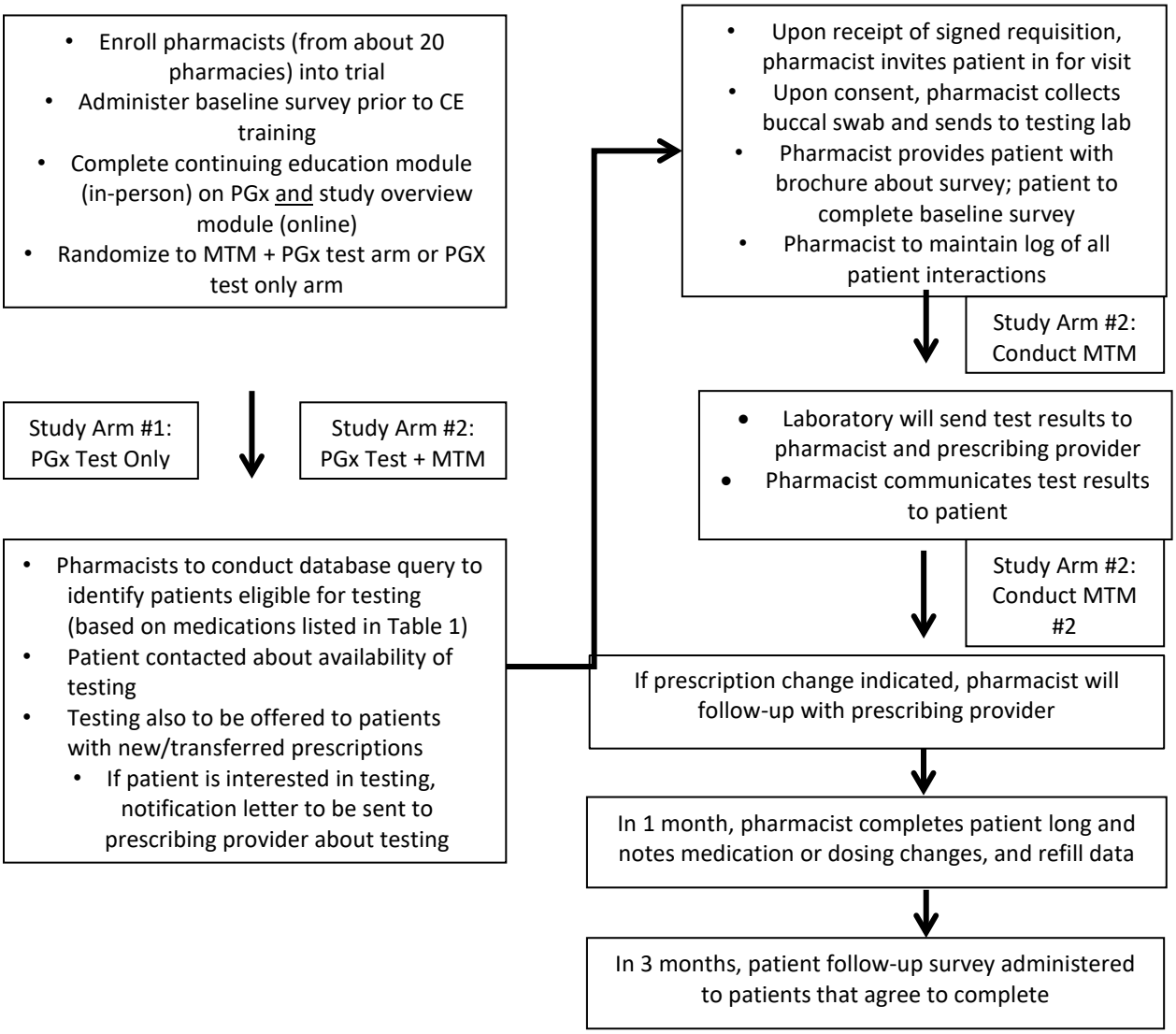
Continuing education (CE) courses on genetic testing and pharmacogenetics have been demonstrated to be an effective way to introduce new applications and even increase personal interest for providers (The Royal Society, 2005; Netzer & Biller-Andorno, 2004; Buchanan et al, 2002). Based on a survey of North Carolina pharmacists (Pro00062612), respondents prefer to learn about pharmacogenetics using a continuing education program, or online resources. Therefore, we will provide web-based seminars all participating pharmacists. For this study, participating pharmacists will be required to attend a CE session as described below. A second module on MTM will be required only of pharmacists in the MTM arm. All modules will be made available multiple times to accommodate pharmacists' schedules; pharmacists can receive CE credit. In addition, the slide decks will be made available throughout the study as a reference for pharmacists. The PGx CE presentation has been developed by the clinical pharmacist (J. Moaddeb) on our team and has been used as a training module for pharmacists.

- In-person PGx CE & Study Overview (required of all pharmacists): The purpose of this CE is to provide an overview of basic genetic concepts and PGx-informed genomic medicine, including specific applications, highlighting many of the tests for the drugs listed in Table 1; to review test interpretation and sample test reports, strategies to effectively communicate PGx test results with both providers and patients, responses to possible patient questions, and documentation of results in the pharmacy record. The presentation will include an overview of a pharmacist "toolkit" that will be dispensed to each participating pharmacist. In addition, an overview of the study will also be presented, including the timeline, purpose/ significance, patient/pharmacist surveys, contact information of research team, and funding support. Pharmacists must attain an 80% score on a 5-question quiz at the end of the presentation in order to participate in the trial. Consent for pharmacist participation will also be obtained at this time (see section on Pharmacist Consent)

- In-person MTM (required only of pharmacists randomized to MTM + PGx testing arm): The purpose of this CE is to review elements of MTM, development of medication action plans, and incorporation of PGx testing into an MTM session. The development of this module was adapted from the MTM module offered by the American Pharmacists' Association (APhA). Attendance may be waived if the pharmacist provides proof of completion of the APhA MTM CE program.

PART II. PHARMACOGENETIC TESTING IN COMMUNITY PHARMACY TRIAL

Part II of the study will involve the cluster randomized trial to compare the effect of PGx testing as a stand-alone service to PGx testing with MTM (Figure 1/Aim 2)). We aim to enroll 20 pharmacist (in 20 separate pharmacies) and 360 patients in the study (~18 per pharmacy).



PGx Testing. Testing will be available for patients with active prescriptions for the drugs listed in Table 1. The drugs were selected based on CPIC guidelines and/or drug labels with PGx information that are likely to be filled at community pharmacies. If new CPIC guidelines are developed by the start of the study, we will update the list accordingly. Testing for each of the genes listed in the table will be provided by the CLIA-certified laboratory Pathway Genomics (CLIA # 05D1092505; San Diego, CA). The test for this study is a customized panel test that includes CYP2D6, CYP2C19, CYP2C9, SLC01B1 and VKORC1/CYP2C9. Currently, turnaround time for testing is 7-10 days. Given the varying coverage policies for PGx testing, all test fees will be supported by the study.

Patient eligibility for PGx testing will be determined by the pharmacist and will be done within the context of standard practice at that pharmacy. For patients that express interest in testing, the pharmacist will send a notification letter about the test and the test requisition form to the prescribing provider of the eligible medication for his/her signature. If the provider returns the signed form, pharmacists will invite the patient to the pharmacy to discuss testing. Pharmacists will be encouraged to disseminate the test information sheet to patients when testing is initially discussed (see component #1 of the toolkit); the research study team will provide copies of the handout to each participating pharmacy. The test lab will send the pharmacist an interpretative summary report (genotype and phenotype) and the pharmacist will send a copy of the report to the prescriber on record. The interpretation of test results and communication of results with patients and their prescribing provider are at the sole discretion of the pharmacist. The study pharmacist will be available to the community pharmacists to assist with questions regarding testing processes/procedures, interpretation of results, or treatment recommendations. All pharmacist interactions will be noted for data analysis, including the nature of the interaction and time spent per interaction.

MTM + PGx Testing Arm. A licensed pharmacist will be required to conduct each MTM session in the MTM + PGx study arm. There will be two MTM sessions: MTM #1 will be conducted in-person and MTM #2 will be conducted in-person or by phone. The five core elements of a standard MTM will be included.[32]

- **MTM Session #1:** The MTM session will include review of the patient's medications, the medical history, most recent lab values if available/known, and medication history. Patients will be encouraged to bring a list and, if possible, the actual containers of both prescription and over-the-counter medicines. The information will be recorded in a standardized MTM form (Appendix 3). The pharmacist will document barriers and possible recommendations to increase adherence in the MAP (Appendix 4). At the completion of the session, the pharmacist will review PGx testing, including the purpose of testing, description of test, test limitations, and anticipated outcomes. Pending patient consent for testing as required by the lab, a buccal sample will be collected and sent for testing.
- **MTM Session #2:** The follow-up MTM session will be conducted either in-person or by phone as deemed appropriate by the pharmacist and feasible for the patient to return to the pharmacy. Our experience with pharmacist reporting of PGx test results indicates that results can be discussed in an average of 15 minutes (see section *C.2.a*). Telephonic MTM has been found to be as effective as in-person MTM with respect to outcomes and patient satisfaction.[78-81] Prior

to MTM#2, the pharmacist will review the PGx results and the patient's medication history to determine if drug or dosage adjustments are indicated based on the results. If the patient is taking another medication impacted by one of the PGx genes tested and there is strong evidence regarding dose adjustment/drug selection based on genotype, recommendations for additional drug changes/dose adjustments will also be communicated to the patient and ordering provider. The patient and pharmacist will review the information provided in the previous session, possible medication changes, PGx test results and its significance to current treatments, and strategies to improve adherence. The pharmacist will also discuss how the results may be important for future medications. Patients will be provided a copy of the MAP and a summary card of their PGx results will be filled out for the patient to retain. The pharmacist will also contact the prescribing physician with recommendations based on the results and a copy of the MAP. All final treatment decisions will be made by the physician.

Table 1. Drugs eligible for trial

Drug	***Gene***	***CPIC***	***FDA Label***	***Test Interpretation/Utility***
Aripiprazole	*CYP2D6*	No	Yes	The drug's half-life approximately doubles in poor metabolizers compared to extensive; the dose for poor metabolizers should be decreased to minimize side effects.[82,83]
Carisoprodol	*CYP2C19*	No	Yes	Patients with reduced metabolism should use caution while on carisoprodol. Poor metabolizers of CYP2C19 have a 4-fold increase in exposure to carisoprodol and a 50% decreased exposure to meprobamate (a metabolite of carisoprodol) compared to normal CYP2C19 metabolizers[84]
Celecoxib	*CYP2C9*	No	Yes	Half-life was 2.7-fold higher in subjects with CYP2C9 *3/*3 (Poor Metabolizer) than in extensive metabolizers. Patients who are poor CYP2C9 metabolizers should be administered celecoxib with caution and a dose reduction of 50% should be considered.[85]
Citalopram	*CYP2C19*	Yes[86]	Yes	In patients who are poor CYP2C19 metabolizer, a dose reduction of 50% should be considered for a starting dose and titration should be initiated until therapeutic response is reached; an alternative medication may be considered[87]
Clopidogrel	*CYP2C19*	Yes[88]	Yes	Patients, who are poor or intermediate metabolizers of CYP2C19, should consider an alternative medication[89]
Metoprolol	*CYP2D6*	No	Yes	For patients who are poor or intermediate metabolizers of CYP2D6, a dose reduction or an alternative medication should be considered prior to initiating therapy. [90,91]
Nortriptyline	*CYP2D6*	Yes[92]	Yes	For patients who are poor or intermediate metabolizers of CYP2D6, a dose reduction or an alternative medication should be considered prior to initiating therapy
Paroxetine	*CYP2D6*	Yes[86]	Yes	In patients who are poor CYP2D6 metabolizers, a dose reduction of 50% should be considered for starting dose and titration should be initiated until therapeutic response is reached; an alternative medication may be considered

Simvastatin	*SLCO1B1*	Yes[93]	No	Myopathy is a major complaint for patients on statin therapy. Patients with the low functioning genotype (CC) are at risk for myopathy and a different statin should be considered or a low dose should be initiated with continual CK monitoring
Warfarin	*CYP2C9/* *VKORC1*	Yes[94]	Yes	Genetic polymorphisms together with variables like age and body-surface area impact daily dose recommendations, driving dosing algorithms in the drug label. These algorithms aid in providing specific dosage recommendations[95-98]

PGx Testing Only Arm. Participants in this arm will receive only PGx testing. Prior to testing, the pharmacist will review PGx testing with the patient, including the purpose of testing, description of test, test limitations, and anticipated outcomes, using any of the toolkit resources provided as desired/needed. Upon patient consent, a buccal sample will be collected and sent for PGx testing. When testing is completed, the pharmacist will review the PGx results and the participant's medication history to determine if drug or dosage adjustments should be considered based on the test results. Results may be provided to the patient using the PGx wallet card or patient test report provided in the toolkit. If the patient is taking another medication impacted by the same PGx gene and there is strong evidence regarding dose adjustment/drug selection based on genotype, recommendations for additional drug or dosing changes will be made. The pharmacist will contact all patients to discuss their result, even for patients with a "normal" test report, and if any changes to their medications are indicated. The pharmacist will also contact the participant's provider if changes are indicated. In the event that MTM is clinically indicated for a patient who undergoes PGx testing in this arm, pharmacists should provide the service and we will exclude these patients from the study.

Pharmacist Study Population. A total of 20 pharmacists working in independent community pharmacy settings in North Carolina who are members of the Community Pharmacist Pharmacogenetics Network (CPPN) will be eligible to participate in the cluster randomized trial. CPPN is a collection of community pharmacists in North Carolina who are currently offering or interested in offering PGx testing. Network members enroll with the understanding that they will be contacted regarding potential research studies. In addition, community pharmacies can be referred by CPPN members or contact the study investigator if interested in participating in the study. If additional recruitment is necessary, study staff will contact pharmacist using contact information provided via a mailing list from the North Carolina Board of Pharmacy. No prior experience with PGx testing is required. Pharmacies interested in participating in the MTM + PGx arm will be asked to confirm that they have obtained APhA training or will/have completed our in-person training module on MTM + PGx and have private space in the pharmacy to deliver MTM. If more than 10 pharmacies capable of offering MTM are interested in serving as a study site, we will randomly assign them to a study arm. For each pharmacy, we will request that a single pharmacist be assigned to the study. All pharmacists must participate in the PGx training session prior to patient enrollment and meet with the study pharmacist/study clinical coordinator to review the study protocol.

Patient Study Population. All patients seen by participating pharmacists will be eligible to participate in the study. Patients must be 18 years or older, able to consent to testing on their own

and can read and write in English, and have a new or existing prescription (<1 year active) for a drug listed in Table 1 to be eligible to participate. Each pharmacy will identify existing patients eligible for testing through a query of their database for active prescriptions for the selected drugs. If more than 30 patients in a pharmacy are identified by the database search, we will ask pharmacists to contact patients with the newest prescriptions. Patients will be contacted by phone or in-person by the pharmacist to introduce the study. Interested patients will be asked to visit the pharmacy to learn more about testing, sign the consent form requested by the testing laboratory, and provide a DNA sample (buccal swab). Patients who have had PGx testing for one of the genes in Table 1 or had an MTM within the past 12 months will be ineligible. All women and minorities who meet the study inclusion criteria will be eligible to participate in the study. Based on our power calculations, we estimate that we would need to enroll 18 patients per cluster (*360* total).

Patients who consent to testing based on their pharmacist's recommendation will be asked to provide a buccal swab for DNA extraction. Patient samples will be sent for testing to Pathway Genomics laboratory. Testing will be provided at no cost for participants. As the Pathway Genomics' clinical tests are currently available to any clinician, only the consent required by the testing lab will be required of the patient.

Patients in the control arms will be identified by each participating pharmacy; two controls will be identied per each participant in the PGx arms (2:1) and matched on drug, age and gender. Time on treatment, medication changes (dose/drug selection), and refill history (adherence) data will be collected along with demographic data and compared to patients in the PGx testing arms. Based on their pharmacy records, patients who have undergone MTM or PGx testing outside of the study will be excluded from the control arm.

Risk/Benefit Assessment. If patients decide to have pharmacogenetic testing, a buccal swab sample is required. There are no known risks to a buccal swab sample. The sample, or DNA extracted from the sample, will be sent to the laboratory and stored only for the time necessary laboratory regulations.

The test results may be used to inform treatment decisions and also impact patient behavior regarding medication adherence. Potential negative consequences of testing for patients may include increased worry about one's health status and the health of relatives, negative emotional reactions, and familial implications. Study investigators will provide information to pharmacists regarding the Genetic Information Nondiscrimination Act (GINA) as part of the information in components of the toolkit; pharmacists will be encouraged to share this information with patients during discussion about testing.

Informed Consent for Pharmacists. Pharmacists will be invited to participate in the study and will be randomized to the MTM + PGx testing arm or PGx testing arm only. All participating pharmacists will be asked to provide informed consent by signing a study consent form that will be reviewed with them by the study pharmacist at the time of the provision of the CE and other educational materials (A consent form for pharmacists has been submitted for IRB review)

Informed Consent for Patients. Consent for testing will be obtained from patients as required by the testing company per standard clinical practice. Patient educational materials will be provided to facilitate discussion of testing with patients and informed decision-making. Pharmacists will be asked to disclose that this testing is being made available at no cost to the patient or their insurer as the pharmacy is participating in a research study looking at the delivery of these tests in a pharmacy setting that is supported by an NIH grant. The test itself is not under investigation and is offered by several major commercial clinical testing laboratories, therefore, a research consent is not required for testing (consent will be required for surveys, see Part III).

Incentive. Pharmacies in the PGx testing arm will receive a $1,500 honorarium and pharmacies in the PGx + MTM testing arm will receive a slightly higher honorarium ($2,000) given the additional effort required. Pharmacogenetic testing and MTM services will be provided at no cost to patients. Upon completion of the surveys (see next section), incentives will be offered to both pharmacist and patients.

PART III. SURVEYS

The integration of PGx testing into the community pharmacy setting will be assessed primarily through surveys of patients and pharmacists. In addition, we will conduct semi-structured interviews with a subset of pharmacists to gather more in-depth understanding of their experiences, perceived barriers, and likelihood to continue to offer PGx testing. The measures to be assessed are described below; clinical outcome measures will be collected about the medications impacted by PGx only.

Patient Surveys *(Aim 2b)* The baseline survey will collect demographic data, prior knowledge about PGx, self-reported co-medications, time on treatment for PGx-related drug(s), and medication adherence (see Table 2; Appendix 5). The follow-up survey will gather data on 1) satisfaction with the testing experience in a pharmacy setting, including use/provision of patient materials from Aim 1; 2) perceived value of testing; and 3) comprehension of test result. Additional measures include medication-taking behaviors and information-sharing. The follow-up survey will be administered approximately one month after the PGx results are communicated since many of the medications are prescribed in 90-day allotments. Key survey questions are further described below; data on age, gender, co-medications, and time on treatment for PGx-related drug(s) will also be collected for controls.

- [Baseline] Literacy. We will screen for health literacy using the validated single question: "How confident are you filling out forms by yourself?" Compared to the gold standard literacy tools REALM or S-TOFHLA, this single question accurately predicts inadequate health literacy [99] and is more feasible to administer.
- [Follow-up] Comprehension of Results. Our primary outcome will be comprehension of test results based on gist recall of the phenotype.[100] Specifically, the outcome of interest is the patient's recognition of the presence or absence of a variant gene. Due to the complexity of genotypes and presumed patient unfamiliarity with gene nomenclature, we do not believe it reasonable to expect patients to recall their genotype. Therefore, we will instead ask patients to circle their specific metabolizer status (e.g., rapid, extensive, intermediate, poor, or inconclusive). For the genes *SLCO1B1* and *VKORC1*, we will ask patients to indicate their test

report found that they carried a known variant allele or not. We and others have used this approach to assess patient comprehension of genetic test results.[101,102] The primary endpoint for comprehension is dichotomous (correct/incorrect). To assess patients' understanding of the significance of the result to their care, we will ask if the pharmacist recommended any changes to their treatment based on test result. Responses will be compared to the test results reported in the pharmacist's patient log (see below) and recommended pharmacist changes.

- [Follow-up] Satisfaction with Testing Experience. To assess patients' perceived value and satisfaction with PGx testing, we will ask about their likelihood to have PGx testing again in the community pharmacy setting. A survey tool from Walker et al.[103] will be adapted to gain further information about participant satisfaction. These questions have scale outcomes and will be treated as continuous variables.
- [Follow-up] Perceived Value of Testing. We will assess the perceived impact of the PGx test result on patients' confidence in the safety and effectiveness of the prescribed drug. A PGx result may be perceived as 'good' or favorable' if it is believed to inform selection of a safe drug or dosage adjustment. However, some patients may perceive the result as less than favorable if they are found to be a poor metabolizer and a lower dose is needed to reduce risk of side effects. Such patients may feel that the lower dose will be ineffective, and potentially fail to adhere to the drug regimen. In addition, we will assess participants' likelihood to pay for future PGx testing as a surrogate measure for perceived value.
- [Baseline & Follow-up] Several secondary clinical outcomes will be measured to assess overall impact of PGx testing during the follow-up survey including information-seeking about side effects of new drugs and medication adherence. To assess medication adherence, we will use a combination of survey tools and refill data from the pharmacies. Participants will be asked to complete the validated Beliefs about Medicines Questionnaire (BMQ)[104] and Voils medication adherence scale (https://sites.duke.edu/corrinevoils/versions-of-scale/). Higher concerns and lower necessity measured by the BMQ have been associated with poorer medication adherence.[105,107] Although the MMA scale is generally the more accepted tool for self-reported adherence, the BMQ scores can be used as a covariate to determine reasons for non-adherence (e.g., poor satisfaction). In addition, we will assess the psychological impact of testing using the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire.[108] The total score on anxiety and distress subscales range 0 to 105 with a higher score indicating more distress. No studies have defined a cut-off value for high distress; therefore, we will follow the approach by Bjornslett et al[109], and define high distress as a MICRA score above the mean +1 standard deviation.

Pharmacist Patient Log. We will ask pharmacists to keep track of their interactions with each patient to enable analysis of feasibility of delivery of PGx testing in a pharmacy setting and compare responses between pharmacy and patient surveys (see Appendix 7). In particular, we will ask pharmacists to document reason for each interaction with a patient, time spent addressing interaction, whether by phone or in-person, the test result, time spent following up with patient's provider, whether any drug or dosing adjustments were made based on the test result, and refill data. Pharmacy adherence data will extend 6 months after test results are communicated. Two measures of adherence based on data from the pharmacy will be generated: 1) the proportion of days covered[110-112] (PDC; # of days with drug on-hand]/[# of days in the specified time interval] (x 100)]; and 2) medication possession ratio (MPR; # of days of

medication supplied within the refill interval/# of days in refill interval). Patient-reported adherence data will be collected at baseline and 1 month following receipt of test results. The log record will be stored in a folder with the patient's name in the pharmacy; at the completion of the study, once the log record is returned to the research team, the log record will be coded and the folder will be destroyed so that the research team will have no patient identifier.

No identifying information will be collected on the patient logs. Forms will be kept in the pharmacy in a folder with the patient's name and any other relevant information noted by the pharmacist. At the completion of the study when the log is picked up by the research team, the folder will be discarded and all forms will be labeled with a study ID# number. A code will be established and accessible only to the clinical research coordinator and PI.

Pharmacist Surveys. Participating pharmacists will be asked to complete two surveys (Appendix 6). First, a baseline survey will be administered to all pharmacists prior to participation in the CE training. The baseline survey will assess knowledge of and experience with PGx testing, comfort with integrating PGx testing into pharmacy practice, comfort discussing PGx testing with patients, and experience with patient education and MTM. Pharmacist and pharmacy practice data will be collected including number of years in practice, other pharmacy services offered, and estimated time to complete each service. Second, we will administer a survey at the completion of the study to re-evaluate knowledge of PGx testing, comfort with integrating PGx testing into pharmacy practice, and comfort discussing PGx testing with patients. In addition, we will ask about the likelihood of adding PGx testing to their pharmacy services and major barriers to implementation including potential impact of adding this service on other currently offered services.

Table 2. Outline of proposed survey content for pharmacists and patients.

Pharmacists	**Patients**
<u>Baseline Survey (Pre-Study- Prior to CE Training)</u> I. Background (Pharmacist) II. Background (Pharmacy) III. Experience with PGx testing IV. Knowledge/Awareness of PGx testing V. Experience with patient education and MTM <u>Follow-Up Survey (Post-Study)</u> I. Re-evaluate knowledge of PGx testing II. Comfort with providing PGx testing in pharmacy practice III. Likelihood of adding PGx testing to their pharmacy services/perceived barriers to implementation	<u>Baseline Survey (following Consent for PGx Testing)</u> I. Demographics II. Health Literacy Screening/Perceived Knowledge of Genetics & Drug Response III. Medication adherence behaviors (MMA & BMQ) <u>Follow-up Survey (following Communication of Test Results)</u> I. Comprehension of test results and significance to treatment II. Satisfaction with delivery of PGx testing in community pharmacy III. Likelihood to have PGx testing again in community pharmacy/Perceived benefits/value of PGx testing IV. Sharing of test results with other health professionals V. Medication adherence behaviors (MMA/BMQ)

Patient and Pharmacist Survey Pilot-Testing. The surveys will contain a combination of new

and validated survey questions. We will pilot the patient baseline and follow-up surveys on 5 random patients recruited from the pharmacy locations to evaluate understandability of questions and responses, clarity of instructions and introductory text, and time to complete the surveys. Patient pilot-testers will be confirmed not to have had PGx testing prior to participation. In addition, the data collected will be scrutinized to ensure that survey skip patterns are functioning as intended and that all questions provide full use of the given response scale options. The pharmacist surveys will be reviewed by a group of pharmacists not affiliated with the study to assess comprehension and completeness of answer choices. Following analysis of the pre-testing evaluations, the survey instruments will be revised accordingly. If significant revisions are made, another round of pre-testing will be conducted.

Patient Study Population. Patients will be invited to complete two surveys: 1) a baseline survey after they consent to testing and 2) a follow-up survey after they receive the test results. A brochure will be provided to the patient that will describe the purpose of the survey, risks and benefits, participant rights, investigator contact information, and how to access the survey. The pharmacist can ask if the patient would be willing to be contacted by the study coordinator or to complete the survey on their own time online. Upon completion of the baseline survey, participants will be asked to indicate if they would be interested in participating in the follow-up survey and re-contacted.

Pharmacist Study Population. Participating pharmacists will be invited to complete the baseline survey prior to the start of the in-person training session. The instructor (the clinical pharmacist on the research team) will describe the purpose of the survey, risks and benefits, participant rights, investigator contact information, and how to access the survey online (paper copy will also be available upon request). For the post-study interviews, pharmacists will be contacted at the completion of the study to ascertain interest to be interviewed.

Survey Administration. We will use Redcap, an online survey tool to design and administer the surveys. Redcap offers features that allow for custom designs, branching/skip logic, randomization of answer choices, multiple collection features and data output formats. A customized link will be sent to each participant to access the survey set, enabling the study coordinator to track and link responses between survey sets and to send reminders to only those who do not respond. Paper or phone option will be made available as requested; pharmacies can elect which method they prefer at the start of the study.

Pharmacist Semi-Structured Interviews. To complement the survey data and gather more in-depth feedback, we will conduct semi-structured interviews with a subset of pharmacists at the end of the study. The goal of the interview will be to elucidate in greater detail pharmacists' experience in delivering PGx testing, perceived value of testing, consumer interest and likelihood of adding PGx testing as a permanent service. An interview guide will be used to ensure consistency of interviews (Appendix 8). We will aim to interview approximately 20 pharmacists (10/study arm) or until we observe that no further new data are being gathered (saturation of themes). All interviews will be conducted by phone and recorded. We will especially look for differences in themes between the two study arms.

Incentives. Pharmacists participating in the post-study interview will be offered $100. Patient

participants will be offered $20 for the baseline survey and $30 for completion of the follow-up survey for a total of $50 per participant.

Informed Consent. Online consent for the surveys will be obtained from both patients and pharmacists using an abbreviated consent statement presenting the study objective, benefits and risks, and participant rights (abbreviated consent statements to be used for the online surveys for patients and pharmacists have been submitted to the IRB for review). This information will be displayed on the welcome page of the survey; participants must type in their name to affirm that they have reviewed the information and consent to participate in the survey by clicking the appropriate box at the bottom of the page. Only after clicking on the consent box, participants will be able to access the survey questions. Their name will be deleted from the survey responses and replaced with a study ID# number.

For the pharmacist interviews, a verbal consent will be obtained since the interviews will be conducted by phone (a consent statement to be read to the participant over the phone and a Waiver of Documentation of Consent have been submitted to the IRB for review). The interviewer will describe the study objectives, benefits and risks, and participant rights. Participants must acknowledge their consent to have the interview audio-recorded.

Risk/Benefit Assessment. We estimate that the survey poses no risk of physical harm. A potential risk to subjects is that of loss of confidentiality. Every effort will be made to maintain participant information in a private and safe manner to prevent the loss of confidentiality such as the use of coded identification numbers on all research documents and files.

Participants may benefit from the awareness that they have contributed to the current knowledge in the scientific community about the delivery of PGx testing. Collective data gained from this study will add to the general knowledge about pharmacists and patient understanding of PGx testing, effective risk communication strategies, satisfaction with delivery strategy, and impact of testing. Overall, the potential value of the study outweighs the potential risks to which the subjects might be exposed. Participants will be encouraged to speak with the investigator if they have any concerns or questions regarding the study.

Costs to the Subject. There will be no monetary costs to subjects for study participation.

DATA ANALYSIS

Survey Data Analysis. Analysis of data collected from surveys will be conducted using a software package such as STATA. We will calculate frequency data and statistical associations for the respondent characteristics. Both univariate and multivariate analyses will be conducted for hypotheses (see below). Because the trial uses a cluster design, the analysis will use logistic mixed effects regressions by including treatments as the fixed effect of interest and clusters as random effect. We will first test if the random effect is significant or not. If not, then we will use regular logistic regression to perform the analysis; if significant, we will continue using mixed effect logistic model. In either case, odds ratios and 95% confidence intervals will be generated to assess strength of associations between treatments and outcomes. A secondary analysis will be performed in which the comprehension outcome is not collapsed into "correctly identifying the presence of any variant versus no variants", but will include correctly indicating the result for each gene (e.g., slow/fast metabolism vs. average). In this case, a logistic random effects model will also be applied with pharmacist and patient as random effects. If a sufficient number of patients are enrolled per drug, a stratified data analysis by drug will be performed to detect any differences regarding comprehension, adherence, or satisfaction. In addition, the impact of time to treatment will be assessed on patient satisfaction and adherence.

- We hypothesize that patients will have a higher level of comprehension of test results from the MTM plus PGx testing than those receiving testing offered as a stand-alone service.
- We hypothesize that patients overall will be satisfied with PGx testing provided through the community pharmacy and likely to have testing again in this setting
- We hypothesize that patients will find PGx testing beneficial, particularly those who have experienced adverse responses or a poor drug outcome in the past, are taking multiple medications, and are older.
- We hypothesize that patients' increased awareness about their genetic risk to adverse responses will result in improved adherence through assurance about the effectiveness and/or safety of their medications.
- We hypothesize that the additional time required to deliver PGx testing as part of an MTM session may present a barrier to providing PGx testing through this approach.

Sensitivity analyses will be performed to examine the impact of reported changes in comprehension, as individuals who drop out could potentially be less likely to change behaviors. The results of complete case and imputed analyses will be reported. The type of missing data will be examined to understand whether they are missing at random (MAR) or not. If they are, then the assumption will be that the imputed analyses provide the better estimate of the treatment differences. If the decision is that one cannot say that the data were MAR, then both results will be presented with accompanying text describing the potential biases in both sets of results, the level and type of missingness seen, as well as the limitations of interpretations if a significant number of observations were missing.

STUDY SAFETY MEASURES

Safety Measures
This study does not contain any safety endpoint measures.

Pregnancy Guidelines
Pregnant females are eligible to participate in this study if they meet the inclusion criteria. There is no known risk to the mother or unborn child as a result of this study.

Safety Monitoring
Federal regulations require prompt reporting to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head of unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study at DUHS. (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)).
Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the study team to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The Principal Investigator will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. The Principal Investigator or designee will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

Data Safety and Monitoring Plan. We do not believe that a data safety and monitoring board will be necessary for the level of risk posed by this study. Instead, we propose to establish a data safety and monitoring plan that will constitute a review by a panel of pharmacists and physicians (not affiliated with the study) of a random sample of pharmacist consults in the study to ensure the pharmacist is providing accurate, evidence-based advice. In our regular email communications with the pharmacists, we will remind pharmacists to contact us with any questions as they begin offer testing to their patients and also remind them that the study pharmacist is available to answer any questions. The PI or the study coordinator is also available to answer questions. In addition, we will visit a subset of pharmacies during the second week and fourth week after launch of the study and review the logs of the initial 3 patients enrolled. After the first month of the study, we will query all pharmacies to provide information about the number of patients approached and consented. Pharmacy visits and reporting requirements carried out during the study will ensure that pharmacists are enrolling eligible patients and have not encountered any problems in offering PGx testing with or without MTM and that the patient logs are being completed accurately. The follow-up patient survey (administered at 1 month after receiving the test results) will include questions regarding the psychological impact of the test

results for the patient using the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire.[108] The total score on anxiety and distress subscales range 0 to 105 with a higher score indicating more distress. No studies have defined a cut-off value for high distress; therefore, we will follow the approach by Bjornslett et al[109], and define high distress as a MICRA score above the mean +1 standard deviation. All findings from our communications with the pharmacists, the in-person visits, and monitoring of patient testing will be provided to this panel for review.

Documentation of Adverse Events

The investigator is responsible for documenting all AEs observed during the study and follow-up period. Patients will be monitored for adverse events and events will be reviewed by the Principal Investigator and reported based on local and federal guidelines.

- **Definition of AE:** An AE is the development of an unfavorable or unintended sign, symptom, disease or the deterioration of a pre-existing condition that occurs while a patient is enrolled on a clinical trial, whether the event is considered related or unrelated to the study intervention. An adverse event is any adverse change from the patient's baseline (pre-intervention) condition, including any clinical or lab test abnormality that occurs during the course of research after intervention has started.

- **Definition of Unexpected (unanticipated):** Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.

Reporting of Adverse Events

All adverse clinical experiences, whether revealed by observation or other diagnostic procedures by the investigator, or reported by the patient, must be recorded regardless of intervention or suspected causal relationship. Information for the adverse event should include a description with details as to the duration and intensity of each event, the causal relationship to the study intervention, the action take with respect to the study intervention, and the patient's outcome. Any adverse event that is expected, not serious or not related to the research study should be reported as part of the routine clinical data. All adverse events should be recorded in a case report form. Adverse events must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations.

Patients having adverse events will be monitored with relevant clinical assessments and laboratory tests as determined by the investigator. All adverse events are to be followed to satisfactory resolution or stabilization of the event(s).

Any actions taken and follow-up results must be recorded on the appropriate page of the case report form as well as the patient's source documentation (case report).

For all adverse events that require the patient to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at clinically appropriate intervals until satisfactory resolutions or stabilization of the event(s).

Adverse events are to be reported for 30 days after the patient's last experience with the study intervention and for any events beyond that time in which the investigator believes the event is related to study intervention or study related procedures.

Documentation of Serious Adverse Events (SAEs)
The investigator is responsible for documenting all SAEs observed during the study and follow-up period. Patients will be monitored for adverse events and events will be reviewed by the Principal Investigator and reported based on local and federal guidelines.

Definition of Serious Adverse Event (SAE): An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or causes prolongation of existing hospitalization;
- Results in significant or persistent disability or incapacity (defined as a short or long term, temporary, chronic or permanent disruption of the patient's ability to carry out normal life functions);
- Is a congenital anomaly or birth defect;
- Results in the development of drug dependency or drug abuse; or
- Is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical or surgical) to prevent one of the other serious outcomes listed in the above definition). Examples of such events include, but are not limited to intensive intervention in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

Hospitalizations for elective surgery or routine clinical procedure (such as for study intervention administration) that are not the result of an adverse experience (e.g. elective surgery for a pre-existing condition) are not considered SAE's and should be recorded on the appropriate case report form. Hospitalization and/or death that are unequivocally due to progression of disease should not be reported as an SAE.

Serious adverse event collection begins after the patient has signed informed consent and has received a study intervention. If a patient experiences an SAE after signing informed consent, but prior to receiving study intervention, the event will normally NOT be collected unless the investigator believes the event may have been caused by a protocol procedure.

SAEs will be collected for 30 days after the last experience with the study intervention, and serious adverse events occurring 30 days after a patient is discontinued from the study will NOT be

reported unless the investigator feels that the event may have been caused by the study intervention or a protocol procedure.

Reporting of Serious Adverse Events
Study site personnel must alert the principal investigator immediately of any SAEs experienced by a patient. In addition, adverse events must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations. Appropriate reporting to the Duke University Medical Center IRB will be made.

Only adverse events that are deemed to be serious, unexpected and related, or possibly related to the research must be reported to the Duke Institutional Review Board (IRB) in accordance with institutional policy.

If the investigator learns of any SAE, including death or congenital abnormality at any time after a patient has been discharged from the study, and he/she considers the event reasonable related to the study intervention, the investigator should promptly file a report.

Unanticipated Problem Involving Risks to Subjects or Others
Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) will be recorded as required on the appropriate Duke IRB Form. A UPIRTSO is any incident, experience, or outcome that meets all of the following criteria:
(a) unanticipated (defined above)
(b) related or possibly related to participation in the research (possibly related is defined above), and
(c) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
Such an incident, experience or outcome, which includes a serious adverse event, must indicate a significant worsening of the risk/potential benefit relationship of a research study as originally presented in the protocol approved by the IRB. Thus participation in the research study would be associated with a significantly greater risk and/or reduced benefit than was previously known or recognized. Any such incident, experience or outcome generally will warrant consideration of a corrective action, such as a change in the research protocol and/or consent document, in order to protect the safety, welfare and rights of research subjects.

The reporting of UPIRSO events will follow the IRB guidelines on prompt reporting of UPIRSO.

Follow-Up of Adverse Events and Serious Adverse Events
The investigator is responsible for appropriate medical care of patients during the study. The investigator remains responsible for following, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Quality Assurance & Quality Control

A communication plan has been established to ensure the effective flow of information among study personnel and is as follows. The Principal Investigator is ultimately responsible for communicating the necessary details of this protocol including any amendments, concerns, changes in procedure, or other essential information. Team meetings are held at least monthly for most of the year. Team members that are regularly expected to attend these meetings include but are not limited to a clinical research coordinator, pharmacist, and treating physician from each clinic site in addition to the Principal Investigator or designee.

- Review and evaluate the clinical data and use standard computer edits to detect errors in data collection.
- To ensure accurate, complete, and reliable data, the investigator will perform and/or implement the following tasks as deemed necessary:
- Study staff will cooperate with the monitor and be available during at least a portion of the monitoring visit to answer questions and to provide any missing information.
- Study staff will keep records of laboratory tests, clinical notes, and patient's medical records in the patient's files as original source documents for the study.
- Store and maintain source documents and other materials as required by local regulatory guidelines.
- Perform routine site monitoring
- Maintain ongoing site communication and training
- Perform data management quality control checks and perform continuous data acquisition and cleaning
- Perform internal review of data and appropriate quality control check of the final data

Study files are randomly selected for periodic checking against computerized data by the study coordinator or designee. The data files for recruits who die during the period of follow up will be systematically checked for accuracy and consistency of data entry.

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