Pharmacogenomics

Pilot study of pharmacist-assisted delivery of pharmacogenetic testing in a primary care setting

Aim: To describe the rationale and design of a pilot program to implement and evaluate pharmacogenetic (PGx) testing in a primary care setting. **Study rationale:** Several factors have impeded the uptake of PGx testing, including lack of provider knowledge and challenges with operationalizing PGx testing in a clinical practice setting. **Study design:** We plan to compare two strategies for the implementation of PGx testing: a pharmacist-initiated testing arm compared with a physician-initiated PGx testing arm. Providers in both groups will be required to attend an introduction to PGx seminar. **Anticipated results:** We anticipate that providers in the pharmacist-initiated group will be more likely to order PGx testing than providers in the physician-initiated group. **Conclusion:** Overall, we aim to generate data that will inform an effective delivery model for PGx testing and to facilitate a seamless integration of PGx testing in primary care practices.

Keywords: clinical utility • pharmacist support • pharmacogenetics • pharmacogenetic testing • primary care

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Background

Although genetics has long been recognized to play a role in drug response [1], the tremendous amount of research recently has catapulted understanding of the impact of genetic variation on drug targets and risk of adverse drug response (ADR), leading to the development of several clinical pharmacogenetic (PGx) tests. Genetic variation is estimated to account for 20–95% of the differences in individual responses to medications [2] and 137 drug labels currently include information about the impact of PGx variants [3]. More than half (59%) of the drugs with frequently reported ADRs are metabolized by at least one CYP450 enzyme that is highly polymorphic, resulting in a range of metabolic activity [4]. Thus, analysis of particular genetic variants through PGx testing may help optimize pharmaceutical therapy by identifying patients with these polymorphisms and better informing the selection of the proper drug and dosage and reducing risk of ADRs. The substantial healthcare costs associated with ADRs [5–8],

the increasing use of prescription drugs in the USA [9] and other potential benefits of PGx testing such as increased medication adherence [10,11] provide further support for the use of PGx testing to personalize care.

Uptake and use of new clinical applications are determined by numerous factors [12] and many groups are developing and testing tailored implementation strategies to maximize uptake and appropriate use. Health providers have expressed interest in applying new genetic technologies to improve therapeutic decision-making [13–15], including PGx testing. Primary care providers (PCPs) prescribe a substantial proportion of drugs [16,17], many known to be impacted by PGx variants [17–20]. For example, one study estimated that 29% of patients in primary care practices were taking at least one of 16 drugs that are metabolized by the polymorphic CYP450 enzymes [20]. Thus, primary care patients may particularly benefit from PGx testing [21]. However, utilization of PGx tests has been limited, reportedly owing to

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lack of provider awareness about available tests, lack of knowledge about genetics and drug response [22–27], lack of conclusive evidence of clinical utility [28], and concerns regarding coverage and reimbursement [29]. In addition, it is uncertain how PGx testing may be most effectively integrated into the current healthcare system. Testing may be ordered upon initiation of a particular drug or prospectively, as part of routine examination, each with their own advantages and disadvantages including potential delay of treatment and reimbursement [30]. Some pharmacy benefit managers have promoted PGx testing [31]; although healthcare providers still appear uncertain about the use of the test results [32]. Overall, the integration of PGx testing has been slower than anticipated.

To address some of the barriers to the use of PGx testing in the primary care setting, particularly provider knowledge and operationalization, we developed a study to implement and evaluate two educational and clinical support interventions to facilitate integration of PGx testing into primary care: provider-initiated and pharmacist-initiated PGx testing. Both interventional strategies include provider education, but one arm is a provider-initiated PGx testing program with on-call pharmacist support and the other is a pharmacist-initiated PGx testing program with a clinic-based pharmacist making suggestions for PGx testing at the point of care. In this paper, we describe the study rationale, study design and outcome assessments.

Study rationale

While the translational framework of genomic medicine has been described optimally as four sequential phases (gene discovery to health application to evidence-based guidelines to health practice to health impact) [33], the practical translation (in a nonresearch setting) is more difficult to define owing to multiple potential paths and other challenges. The integration of PGx testing into clinical practice will not only require careful consideration of effects on physician practices (particularly with respect to any additional time needed to consent and/or communicate results to patients, which may ultimately serve as a barrier to uptake of PGx testing), but also on the impact of test results on patient behaviors, such as medication adherence. Using two potential delivery systems, this study aims to address the barrier of limited physician knowledge about PGx, as well as operational issues (e.g., when to order testing, from what laboratory and for which drug). We have chosen to focus on primary care practices given the extensive number of drugs impacted by PGx variants prescribed in these settings, the potential to substantially improve treatment for a large number of patients and the paucity of studies in this important community.

Study design

The study aims to assess two delivery models of PGx testing for commonly prescribed drugs in primary care practices and to evaluate the delivery of testing from three perspectives: physician, patient and practice setting. As shown in Figure 1, the study aims to compare a 6-month intervention in which physicians order PGx testing according to their delivery system (pharmacist initiated or physician initiated), and surveying participating physicians and patients for whom testing was ordered at two time points in the study. We chose to have a pharmacist serve as the main clinical decision support for providers in the primary care practices during the intervention period given their experience with providing many different clinical services within different practice settings [34,35] and their knowledge and training in pharmacokinetics and pharmacodynamics, including PGx. In addition, pharmacists have played an instrumental role in the delivery of PGx testing in other clinic settings [36,37]. Prior to the start of the intervention period, all providers are required to attend an educational session about PGx. The study has been approved by the Duke University Health System Institutional Review Board and registered at clinicaltrials.gov (NCT01600846).

Provider education

Two types of provider education/support were developed for the study: printed/online materials and a continuing medical education (CME) presentation. As CME courses on genetics and PGx have been demonstrated to be an effective way to introduce new applications and even increase personal interest [38–42], we developed a 1-h CME-accredited presentation on PGx testing presented by one of the investigators (G Ginsburg and A Cho). The CME presentation is required for all physician participants. The learning objectives of the CME presentation include genetic processes and terminology, history of pharmacogenetics, two PGx case studies (warfarin and codeine), overview of recommendations and clinical guidelines from the US FDA, and relevant ethical, legal and social issues. Printed resources are also provided, including a pocket guide of each of the drugs for which PGx testing is provided in the study, information about the major genetic variants in the relevant genes, and how the test result could impact drug selection or dosing. For more convenient access, the information in the pocket guide as well as additional resources was also available online. Additionally, in order to assist providers in discussing PGx testing with their patient, an educational brochure was developed to be given to patients describing personalized medicine, and specifically PGx testing. The patient materials were evaluated and revised
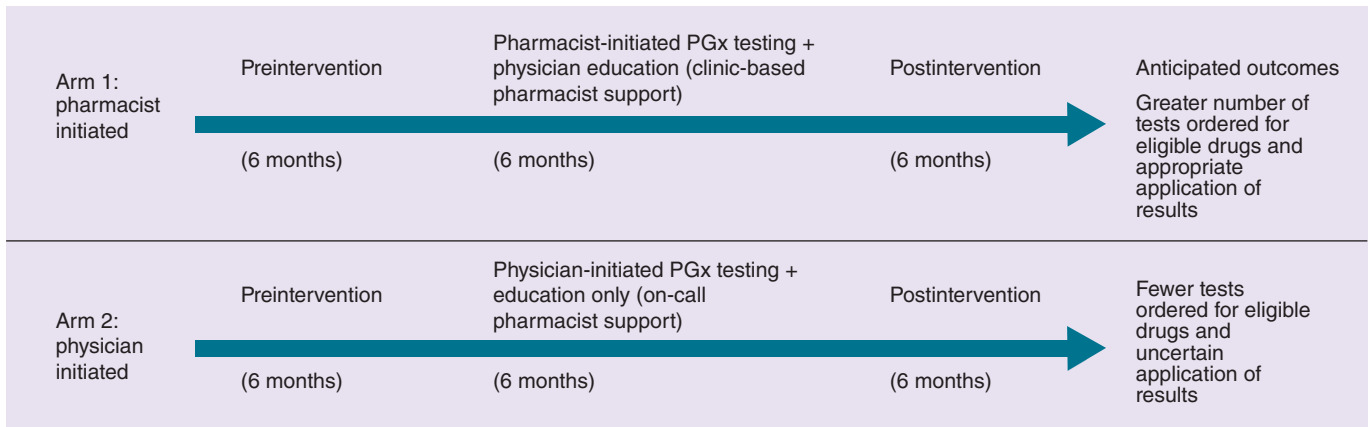
Figure 1. Overview of pharmacogenetic delivery model study design and timeline.
PGx: Pharmacogenetic.

through a series of cognitive interviews conducted with 12 members of the public, recruited from Durham, NC, USA, prior to being used by providers.

PGx testing

A total of six genetic tests associated with the metabolism of 12 drugs are available in this study: *CYP2D6, CYP2C19, HLA-B*1502, CYP2C9, SLC01B1* and *VKORC1/CYP2C9* (Table 1). We selected these 12 drugs based on the list of 16 ADR-associated medications identified by Grice *et al.* [18] and commonly prescribed drugs used in primary care. All but one of the eligible medications for the study included PGx information in the drug label [3]. The one drug that did not have PGx information in the drug label was simvastatin; however, multiple papers have validated the association of the *SLCOB1* variant and risk of myopathy [43–46]. With the prevalent use of statins in the primary care setting, it was thus deemed an important drug to include in the study. In addition, 58% of these medications listed had Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines available to further aid in optimizing drug therapy for the patient. Furthermore, the medications listed in Table 1 were selected based off the Table of Pharmacogenomic Biomarkers in Drug Labeling [3]. A saliva sample for DNA extraction is collected using the Oragene-DNA® kit from patients who consented to testing based on their physician's recommendation. All testing is performed by the Mayo Medical Laboratory (MN, USA).

Testing is provided at no cost to the patient for select drugs with PGx evidence to support adjustment to drug or dosing decisions. We recognize that covering the costs of testing may artificially increase use of testing. However, given the uneven coverage of testing in the US by public and private insurers [47], the study population would be potentially biased to those patients with insurance coverage or able to afford

testing expenses out-of-pocket without enabling all patients access to testing if indicated.

Pharmacist-initiated intervention

In the pharmacist-initiated intervention, a pharmacist is based at the practice location to screen patients prescribed a new targeted medication during their clinic visit and provide on-site consultation to providers about testing. Specifically, the pharmacist alerts the provider about the availability of PGx testing for patients prescribed one of the targeted drugs via electronic messaging through the electronic medical record. As a result, the provider receives the pharmacist recommendation after the prescription is written, similar to the current pharmacy benefit manager model where notification about testing is carried out after prescribing [48]. Decisions about testing, interpretation of test results, communication of results with patients, and any decision to continue or change therapy are at the sole discretion of the PCP, although physicians can consult the pharmacist with questions. All pharmacist interactions with physicians are noted for data analysis, including the nature of the interaction and time spent per interaction.

Provider-initiated intervention

In the provider-initiated practice, the decision to offer PGx testing is determined by the PCP unassisted by the pharmacist. If contacted by the PCP, the on-call pharmacist provides support and responds to questions or issues related to testing processes/procedures, interpretation of test results and/or treatment recommendation. Decisions about testing, interpretation of test results, communication of results with patients and any decision to continue or change therapy are at the sole discretion of the PCP. All pharmacist interactions with physicians are noted for data analysis, including the nature of the interaction and time spent per interaction.

Table 1. List of medications and genes eligible for the study.

Drug	Gene	CPIC or other guideline available
Codeine	CYP2D6	Yes
Fluoxetine	CYP2D6	No
Nortriptyline	CYP2D6	Yes
Imipramine	CYP2D6	Yes
Metoprolol	CYP2D6	No
Warfarin	VKORC1/CYP2C9	Yes
Clopidogrel	CYP2C19	Yes
Carbamazepine	HLA-B*1502	Yes
Esomeprazole	CYP2C19	No
Atomoxetine	CYP2D6	No
Celecoxib	CYP2C9	No
Simvastatin	SLCO1B1	Yes

For both the pharmacist-initiated and provider-initiated arm, the ordering of PGx testing at the point of care (when medication is needed) may impact decisions about whether to order testing or when/how to incorporate changes to therapeutic decisions. In particular, the turnaround time for test results ranges from 3–7 days and therefore, providers will need to decide if delaying treatment is feasible or medically necessary until the results are available or if they should prescribe a standard or lower dose while awaiting the results.

Study population

Owing to the nature of this study, two groups are considered research participants: PCPs and patients.

Providers

This pilot study focuses on patients and providers from two internal medicine clinics affiliated with Duke University and located in Durham, NC, USA. Both clinics are part of Duke Primary Care, a network of community-based practices. The two clinics have eight and nine full-time physician faculty, respectively. Only providers that attend the CME course are eligible to participate.

Patients

All patients who are offered PGx testing at one of the two primary care clinics are eligible to participate in the study. Patients in both clinics represent a diverse patient population with respect to age, sex, race and payer mix. The clinic for the pharmacist-initiated arm sees approximately 24,000 patients annually; the patient population is predominantly white (72%), black (26%) and Asian (2%), and most are covered by a managed care plan (39%), Blue Cross/Blue

Shield (25%) or Medicare (25%). Most patients are 50–64 years of age (28%); 65% are 65+ and 21% are 35–49 years old. The clinic for the provider-initiated arm serves approximately 21,000 patients annually; most are covered by Medicare (32%), a managed care plan (31%) or Blue Cross/Blue Shield (29%). Eligible patients must be 18 years or older, prescribed a drug listed in Table 1, able to consent on their own, and able to read and write in English.

Assessments

Physician survey

To assess provider attitudes, knowledge and experience of genetic and PGx testing, an online survey is administered to providers prior to the CME session (Supplementary Material; see online at: www.futuremedicine.com/doi/suppl/10.2217/pgs.14.109). Specifically, the preintervention survey includes two questions about provider and practice history (year of graduation from medical school and number of years in practice), and six questions about experience with general genetic testing including how often they ordered genetic diagnostic or susceptibility tests, how often they referred patients to genetic specialists and how comfortable they feel ordering and discussing genetic testing results. A similar set of questions is asked regarding PGx testing specifically. Physicians are also asked about their awareness of PGx testing, where they learned about PGx testing and questions about their perceptions of the usefulness of PGx testing. To assess provider knowledge of genomics and PGx, we developed a nine-question knowledge component. All knowledge questions are multiple choice, two of the questions are based on hypothetical case reports and one is about genetic discrimination protections. The survey also includes eight questions about factors impacting use of PGx testing and clinical support for and education about PGx testing, many adapted from our previous study [15]; in particular, providers are asked about the perceived roles of various providers (physicians, pharmacists and genetic counselors) in the delivery of PGx.

To assess their experience with PGx testing and changes in attitudes and knowledge, a second survey is administered after completion of the intervention phase. All providers who complete the preintervention survey and attend the CME presentation are emailed a link to the online follow-up survey. In the postintervention survey, providers are asked to indicate the perceived value of the CME presentation, the educational materials, and their interactions (if any) with the pharmacist. They are also asked to provide feedback regarding the PGx laboratory test report. Questions regarding providers' perceptions of and

comfort with using PGx testing are slightly modified from the preintervention and repeated to assess change over time. Changes in providers' knowledge about PGx are assessed using the same nine-question survey from preintervention. Providers are asked what barriers they experienced when using PGx testing, factors that could improve/reduce those barriers and their likelihood of continued use of PGx testing after the study. Finally, providers are asked to report their perceptions of patient preferences and value about testing.

Patient survey

To gather data on patient attitudes and experiences with PGx testing, patients are also invited to complete online surveys (Supplementary Material). Providers who discuss PGx testing with eligible patients ask patients to participate in an online survey to gather patient feedback on attitudes and interest in PGx testing, regardless of whether they underwent testing or not. The study brochure developed for patients provides a link to the first online survey. A consent statement at the beginning of the survey provides information about the study, eligibility criteria, a description of participant requirements, associated risks (i.e., loss of confidentiality), benefits, reimbursement and contact information for study staff. If the patient wishes to complete the survey, they are asked to click-through: "To consent to participate and complete the survey, please click below to continue to the next page." Continuing to the survey is an assumption of consent.

The patient survey collects demographic information including gender, age and race. Patients are asked about their personal and family history of side effects from prescribed medication as well as their personal perceived knowledge and familial experience with genetics and genetic testing. In addition, the survey includes questions about patients' beliefs about the need for and related concerns about medications using the validated Beliefs about Medicines Questionnaire (BMQ) [49]. Patients are also asked to report what factors influenced their decision to have or not to have PGx testing. Upon completion of the baseline survey, patients who consent to PGx testing are invited to participate in a follow-up survey 3 months later. Those willing to participate provide contact information and are sent a link via email to complete the online follow-up survey. The goal of the follow-up survey is to understand the patients' experiences with PGx testing including whether or not they received results, how they received them, what changes if any they recalled being made to their care and their general understanding of the results. Their perceptions of PGx are also assessed regarding their satisfaction, trust in the results and perceived helpfulness of the PGx results. Patients'

information-seeking behavior, medication adherence and overall awareness of side effects are also assessed. To measure drug adherence, we use the validated Morisky Medication Adherence Scale [50]. The BMQ instrument is also included in the post-testing survey to assess the impact of PGx testing on patient beliefs or concerns about medication use as well.

Chart review

To assess provider behaviors before, during and after the study with respect to the number of prescriptions written for drugs known to be impacted by PGx variants and the use of PGx testing, patient charts are reviewed at three time points in the study: 6-month preintervention period; 6-month intervention period; and 6-month postintervention period. The preintervention review assesses new and recent (within 1 month of the reviewed date) prescriptions for drugs listed in Table 1, number of PGx tests ordered, by which physician (using a unique identifier code) and for which drugs. The intervention review assesses the effectiveness of the intervention during a 6-month period based on number of PGx tests ordered. Following the intervention period, several data points are to be abstracted from a chart review of patients seen during the intervention period to determine the number of targeted drugs prescribed, the number of patients prescribed targeted drugs, the number of targeted drugs per patient, the number of PGx tests ordered for each drug and for each patient, which physician ordered the test, whether the pharmacist was consulted pre- or post-testing, physician counseling/follow-up visit to discuss test results, and how the results were applied to treatment decisions including whether treatments were changed owing to nonresponse or side effects, and occurrence of drug-related side effects. For many of the drugs on the study medication list, we anticipate that patients newly prescribed these drugs will have a follow-up visit with the provider within several months, and therefore, we expect to be able to capture most of these data. The postintervention review assesses the durability of the intervention through the following data abstractions: the number of new prescriptions for drugs listed in Table 1, the frequency with which PGx testing is ordered, by which provider and for which drugs.

Study measures

Four groups of study measures will be evaluated (Table 2). First, we will evaluate the effectiveness of two delivery models on provider behaviors by assessing change and durability of any changes based on the number of tests ordered, dosage adjustments, adverse responses and drug discontinuations of target drugs

Table 2. Groups of study measures to be evaluated.	
Study categories	**Measures**
Effectiveness of delivery model	Number of tests ordered, changes in drug selection, dosage adjustments, adverse drug reactions and drug discontinuations
Provider knowledge and attitudes	Provider knowledge, perceived value of testing
Patient attitudes and beliefs	Beliefs about medications, information-sharing and seeking behavior, medication adherence and overall awareness of side effects
Economic outcomes	Pharmacist consultation time, costs associated with alternative medications, monitoring costs and adverse drug events

with available PGx testing during the 6-month intervention period compared with the 6 months prior and the 6 months following the intervention. The data to inform these study measures will be obtained through chart review. Given the lack of in-depth knowledge and expertise of most providers regarding PGx testing and in light of their heavy workload, we hypothesize that the pharmacist-initiated approach will result in greater and appropriate use of PGx testing given the hands-on educational approach with the pharmacist providing expert guidance. Thus, through chart reviews, we will gather data on the number of tests ordered during each study phase, for which drugs (to determine if testing was indicated) and how the results were applied to therapeutic decisions.

Second, we will assess and compare provider knowledge, attitudes, perceived value and self-reported use of PGx testing in each practice before completion of the educational CME and after the intervention period. The data obtained from provider surveys will be used assess this group of study measures. We hypothesize that greater utilization will be influenced by increased provider knowledge and awareness of drugs with PGx testing, comfort in discussing PGx testing with patients and applying results to therapeutic decision-making and positive attitudes towards the testing process. We hypothesize that having a pharmacist with expertise in PGx testing as part of the medical team will result in greater physician comfort with test ordering and application of results as compared with the physician-initiated model.

As patient perceptions are increasingly used to assess quality of care [51–53], we will assess the impact of PGx testing on patients with respect to information sharing and seeking, medication adherence and overall awareness of side effects. We will assess their perceived value of PGx testing, potential concerns about testing, and experience with the testing process and impact on care and medication adherence. The patient surveys will be used for this group of measures. While perceived safety or efficacy may increase as a result of PGx testing, we hypothesize that perceptions of drug safety or efficacy may be negatively affected in those with very high or low metabolizing status and therefore, medication adherence may worsen.

Fourth, we will perform an economic analysis to evaluate the costs associated with the physician-initiated and pharmacist-initiated delivery models as well as costs associated with targeted medications, associated monitoring costs, and adverse drug events. We will combine primary data collection and sound costing methods to compare associated costs between the PGx delivery models and between the study's time periods to evaluate changes in costs associated with the PGx delivery models. These comparisons will provide preliminary information about whether potential savings owing to avoided adverse drug events, reduced follow-up care and/or reduced medication costs could offset the costs associated with PGx testing.

Analysis

Data collected through chart review and surveys will be analyzed using a software package such as STATA. We will calculate frequency data for all survey questions, and perform χ^2 to assess associations between respondent characteristics and knowledge and attitudes. Analysis of the association of categorical variables will be performed using Pearson χ^2 tests and Fisher's exact test. Binary variables will be created from the Likert response scales by clustering responses (e.g., very or somewhat likely). Odds ratios and 95% CIs will be generated to assess strength of associations adjusting for covariates. For most drugs, we do not anticipate having adequately large sample sizes, and thus, will combine data between the two clinic sites to analyze for trends regarding physician and patient knowledge and attitudes.

Discussion

In order to determine the effectiveness of delivering and/or incorporating PGx testing into primary

care settings, we seek to evaluate two delivery models of pharmacist-assisted delivery of PGx testing. Pharmacists can serve as valuable members of the clinic or medical home, collaborating with PCPs to perform medication-related assessments, including test ordering, monitoring and adjusting therapies to improve overall patient care, and now PGx consultations [54–56]. Obviously, it will not be practical or cost effective to place a pharmacist in every primary care setting and therefore, other clinical delivery approaches are needed both to assist healthcare providers and perform patient care. To broaden outreach and increase efficiency, one option may be phone-based support by a central pharmacist group to provide both clinical decision support and patient services. As we are assessing in this pilot study, this option may be feasible once PGx testing awareness increases among providers, but in-person consultation may be necessary during the early stages of clinical use. One hospital has implemented a pharmacy on-call assistance program for test interpretation and application, working closely with the molecular testing laboratory [57]. Thus, it is possible that different settings will warrant different clinical decision support and electronic decision support may become a primary tool in initiating PGx testing and dosing medications based on PGx results.

It will be important to consider the costs and outcomes associated with any delivery model and thus, we designed the study to enable prospective analysis of economic factors. The published literature reporting economic outcomes associated with PGx testing is beginning to mature [58,59]. Most of the literature pertains to use of PGx testing in oncology, wherein several studies demonstrate good value with PGx

testing in early breast cancer [60–62] and variable findings for other cancers [63,64]. Several recent papers have focused on the cost–effectiveness of PGx testing in primary care with variable findings about the potential value of specific PGx tests [65–69]. Although the quality of economic evaluations of PGx testing appears to be increasing with more studies based on data from randomized trials [70,71], the lack of robust data on the clinical utility of many PGx tests limits the development of high-quality evidence on their cost–effectiveness [59].

Conclusion

In conclusion, we aim to evaluate delivery models for PGx testing implemented in a primary care clinic. We anticipate that our study will help provide insight about provider barriers to the use of PGx testing and effective approaches to overcome these barriers. Given the number of factors affecting the use of PGx testing, including both provider and health system factors, it is unlikely that a single approach will be sufficient and feasible in all clinical settings. Therefore, different or a combination of approaches may be necessary depending on the clinical setting and resources available. Using data gathered from this study, we hope to inform decisions regarding delivery models for PGx testing and increase the appropriate utilization of PGx.

Future perspective

We expect that the use of PGx testing will increase in the future as testing has more evidence of utility generated. Thus, it is important to explore the potential delivery options of PGx testing to identify effective approaches to facilitate the appropriate use and applications of testing. Pharmacists may serve as effective clini-

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Executive summary

Background & study rationale
- Several factors have been identified as contributing to the slow integration of pharmacogenomic (PGx) testing in clinical care, including provider knowledge and operational issues.
- Integration of PGx testing into clinical practice will not only require careful consideration of effects on physician practices (particularly with respect to any additional time needed to consent and/or communicate results to patients), but also on the impact of test results on patient behaviors, such as medication adherence.

Study design
- The study aims to assess two delivery models of PGx testing (physician initiated and pharmacist initiated) for commonly prescribed drugs in primary care practices and to evaluate the relative impact of the delivery models from three perspectives: physician, patient and practice setting.
- To address provider knowledge barriers, two types of provider education/support will be developed and evaluated in the study: continuing medical education seminar and pharmacist support.
- Four groups of study measures will be evaluated for the provider-initiated and pharmacist-initiated testing delivery models: PGx test ordering and durability of any changes; provider attitudes and knowledge about PGx testing before and after the intervention; impact on patients with respect to information sharing and seeking, medication adherence and overall awareness of side effects; and associated costs with the delivery models, targeted medications, associated monitoring costs and adverse drug events.

cal decision support to PCPs to promote the appropriate use and application of PGx testing. With this study, we will better understand the challenges, benefits and feasibility of integrating PGx into clinical care and using a pharmacist as a first-hand resource for providers.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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