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Challenges and lessons learned from clinical pharmacogenetic implementation of multiple gene–drug pairs across ambulatory care settings

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Abstract

Purpose: Incorporating a patient's genotype into the clinical decision-making process is one approach to precision medicine. The University of Florida (UF) Health Precision Medicine Program is a pharmacist-led multidisciplinary effort that has led the clinical implementation of six gene–drug(s) pairs to date. This study focuses on the challenges encountered and lessons learned with implementing pharmacogenetic testing for three of these: *CYP2D6*- opioids, *CYP2D6*/

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CYP2C19-selective serotonin reuptake inhibitors, and *CYP2C19*-proton pump inhibitors within six pragmatic clinical trials at UF Health and partners.

Methods: We compared common measures collected within each of the pharmacogenetic implementations as well as solicited feedback from stakeholders to identify challenges, successes, and lessons learned.

Results: We identified several challenges related to trial design and implementation, and learned valuable lessons. Most notably, case discussions are effective for prescriber education, prescribers need clear concise guidance on genotype-based actions, having genotype results available at the time of the patient–prescriber encounter helps optimize the ability to act on them, children prefer noninvasive sample collection, and study participants are willing to answer patient-reported outcomes questionnaires if they are not overly burdensome, among others.

Conclusion: The lessons learned from implementing three gene–drug pairs in ambulatory care settings will help shape future pharmacogenetic clinical trials and clinical implementations.

Keywords

pharmacogenetics; pharmacogenomics; implementation; challenges; precision medicine

INTRODUCTION

Pharmacogenetics can individualize patient care by applying genotype results for selected drug metabolizing enzymes, transporters, and/or targets to inform medication decisions. Precision medicine can improve care by incorporating a patient's genotype into the clinical decision-making process.[1] There are numerous resources for clinical evidence and recommendations for individual gene–drug pairs, including US Food and Drug Administration (FDA)–approved labeling (https://www.accessdata.fda.gov/scripts/cder/daf/) and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (https://cpicpgx.org/). However, routine pharmacogenetic testing has been slow to translate to the clinic, likely because of implementation challenges, including lack of prescriber and patient knowledge, barriers to integrating pharmacogenetic information into electronic health records (EHRs), limited clinical outcomes data, cost of testing, and inadequate or variable reimbursement.[2] The University of Florida (UF) Health Precision Medicine Program (PMP) (Gainesville, FL), a member of the National Institutes of Health (NIH)–funded Implementing GeNomics In pracTice (IGNITE) Network, was established in 2011 to improve integration of genomic data into clinical practice.[3]

The UF Health PMP is a pharmacist-led multidisciplinary initiative that has spearheaded clinical implementation of six gene–drug(s) pairs to date, including (in order of implementation) *CYP2C19*-clopidogrel, *TPMT*-thiopurines, *IFNL3* (*IL28B*)-PEGylated interferon α-based regimens, *CYP2D6*-opioids, *CYP2D6*/*CYP2C19*-selective serotonin reuptake inhibitors (SSRIs), and *CYP2C19*-proton pump inhibitors (PPIs).[4,5] To date, more than 4700 clinical pharmacogenetic tests have been ordered at UF Health. UF Health PMP has partnered with medical institutions in Florida, including Moffitt Cancer Center, Nemours Children's Health System, and Florida State University College of Medicine, a partner within the OneFlorida Clinical Research Consortium (http://onefloridaconsortium.org/).

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Although published reports exist describing pharmacogenetic implementations of gene–drug pairs in a single institution,[6–8] there have been few descriptions of larger-scale, coordinated implementations across multiple practice settings. Select UF Health PMP implementations have been conducted across specialty and primary care outpatient clinics in diverse populations. These initiatives offer a unique opportunity to compare the infrastructure, challenges, and lessons learned with various research and clinical strategies among coordinated implementations. The purpose of this study is to (1) identify challenges encountered in pharmacogenetic implementations within coordinated pragmatic trials across practice sites, and (2) summarize lessons learned to shape future trials and clinical implementations.

MATERIALS AND METHODS

We compared common data measures and stakeholder feedback on challenges, successes, and lessons learned for three implementations at UF Health and partner sites: (1) *CYP2D6*-opioids, (2) *CYP2D6*/*CYP2C19*-SSRIs, and (3) *CYP2C19*-PPIs. The study population included participants who provided informed consent and were in the genotype-guided arms of six different pragmatic clinical trials, all approved by the UF institutional review board (IRB), between 2015 and 2017. We do not report on *CYP2C19*-clopidogrel and *TPMT*-thiopurines because they have been previously described[9–12] or on *IFNL3* (*IL28B*)-PEGylated interferon α-based regimens as there was limited clinical *IFNL3* (*IL28B*) testing after the approval of direct-acting antivirals for hepatitis C.

Pragmatic clinical trial data for these implementations were collected and managed using Research Electronic Data Capture (REDCap)[13] for four data categories: (1) trial design (inclusion criteria, recruitment location, use of questionnaires, among others); (2) participant-level demographics (e.g., age, sex, race); (3) genotype (sample collection, gene[s] tested, genotype and phenotype test results, turnaround time [TAT]); and (4) medication usage characteristics for participants with actionable phenotypes. We defined actionable phenotypes as those that guided a recommendation for drug dose or drug therapy change or initiation of a specific medication, based on guidelines or primary literature.[14–17] Phenotype-guided drug therapy recommendations for all protocols were reviewed and approved by a multidisciplinary team at UF Health PMP. For CYP2D6, phenotype was translated from activity score (Table S1),[14] which was determined based on both genotype and concomitant use of CYP2D6 inhibitors as defined by the FDA,[18] to account for phenoconversion (e.g., conversion from *CYP2D6* "normal metabolizer" to "poor metabolizer" secondary to use of a strong CYP2D6 inhibitor, such as bupropion).[19] For CYP2C19, phenotype was determined based on genotype results.

Anecdotal feedback on challenges was solicited via email from stakeholders, including prescribers and research coordinators, with potential solutions to challenges discussed via teleconference. Finally, multiple rounds of electronic and inperson discussions were held among stakeholders to compile a consensus list of challenges, categorized as either clinical trial design or implementation challenges.

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RESULTS

Description of trials

The six pragmatic trials randomized participants to either a genotype-guided or control (usual care) arm. The trials included three studies comparing *CYP2D6* genotype-guided management of opioids;[20,21] two comparing *CYP2C19* genotype-guided dosing of PPIs,[22] and one study of *CYP2D6/CYP2C19* genotype-guided management of SSRIs, with enrollment periods ranging from 5 to 28 months (Table 1). For *CYP2D6*-opioid trials, participants were either prescribed opioid therapy, or the prescriber was considering initiation of opioid treatment. For PPI trials, patients were eligible if they presented with gastroesophageal reflux disease (GERD) symptoms and were taking a PPI or PPI therapy was planned. For the SSRI trial, patients were eligible if there was a need to start or change SSRI *therapy* for depression, anxiety, or obsessive compulsive disorder.

The primary outcome for all trials was patient-reported improvement of symptoms and/or occurrence of side effects via patient-reported outcome (PRO) questionnaires[23–34] in the genotype-guided versus control arm, which have been or will be reported elsewhere.[21,22] Participants completed questionnaires electronically through REDCap,[13] via paper, or with a study coordinator, and each trial administered multiple questionnaires at various time points throughout the study (Table 1).

Sample collection was via buccal or saliva in 4 of 6 trials, and via blood in the remaining 2 trials (*CYP2C19*-PPI at UF Health and *CYP2D6*/*CYP2C19*-SSRI) (Table S2). All *CYP2D6* tests were performed by the UF Health Pathology Laboratory (UFPL) in Gainesville, Florida, a College of American Pathologists–accredited Clinical Laboratory Improvement Amendments-licensed (CAP/CLIA) clinical laboratory, on the Luminex xTAG *CYP2D6* Kit v3 (Austin, X) platform. *CYP2C19* testing was performed by UFPL using Genmark Diagnostic's eSensor XT-8 (Carlsbad, CA) platform for UF Health studies. Nemours Specialty Clinics used either the Spartan RX™ (Ottawa, ON) platform or sent samples out to Nemours Alfred I. DuPont for Children Hospital's CAP/CLIA laboratory, where genotyping was performed by Sanger sequencing on polymerase chain reaction products (Applied Biosystems–Thermo Fisher Inc. Waltham, MA). Alleles tested for *CYP2C19* and *CYP2D6* were consistent across studies using UFPL but differed for *CYP2C19* tests performed at Nemours Specialty Clinics. (Table S2).

Trial design challenges and solutions

Enrollment design—A total of 793 patients were enrolled across all trials, with 469 participants assigned to the genotype-guided arms overall. Individual trial enrollment ranged from 49 to 371 participants in both arms (Table 1). Enrollment occurred over a period ranging from 4 months to two years. Enrollment goals were met in all trials, except for the *CYP2D6*-opioid cancer pain trial, which was terminated early for slow enrollment.

Participants who were enrolled in the genotype-guided arms were mostly Caucasian across all studies (Table 2). Baseline characteristics between genotype-guided arms and control arms were not different except in the two *CYP2D6*-opioids trials in chronic, noncancer pain, which used a cluster design versus randomization at the patient level (data not shown).[21]

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This would suggest that randomizing at the patient level, as opposed to a cluster design, is key for ensuring similar baseline characteristics between comparison groups.

As these trials were pragmatic, minimal exclusion criteria were applied, allowing prescribers to enroll who they wanted tested. This presented as a challenge for some prescribers who reported they struggled with identifying for whom to order pharmacogenetic testing, or determining who would most benefit. The gastrointestinal prescribers' solution was to target patients with refractory GERD, but all prescribers on the post-trial teleconference agreed that an ideal solution would be for potentially appropriate patients to be identified through electronic decision support tools.

Questionnaires—Low completion rates for study questionnaires were challenging for certain trials. Over the duration of the trial, the participant questionnaire completion rate varied between 44% and 98% across trials. The trials ($n = 3$) that administered questionnaires at two time points over the duration of the study had an average completion rate of 97%, as compared with 57% for the trials that administered questionnaires five or more times (Table 2). This suggests that limiting the frequency of questionnaire completion can improve completion rates.

Seven prescribers participated in a post-trial teleconference to provide feedback on challenges encountered during the trials and discuss possible solutions. Of the prescribers on the teleconference, five were involved with the *CYP2D6*-opioid trials, and two were involved with the *CYP2C19*-PPI trial at UF Health specialty clinics. Feedback from the *CYP2D6*/ *CYP2C19*-SSRI trial was obtained via email.

Implementation challenges and solutions

Sample collection and testing—Based on available data, the impact of sample collection method on participant enrollment differed in children as compared with adults. Of the 127 children approached for study enrollment, 60 were offered buccal sample collection; for the remaining 67 children, a blood sample was required because genotyping was only validated in the clinical laboratory at the time for blood. One hundred percent of children offered buccal sample collection consented to enrollment, whereas when blood collection was required, only 73% (49 of 67) of children consented. In adults, data were only available for control participants who consented to genotyping and participation did not differ by sample collection method (89% for buccal and blood). Based on these experiences, we concluded that noninvasive sample collection (e.g., buccal) for children is essential to achieve study enrollment goals, whereas requiring blood collection may not influence participation in adults.

Of the 469 participants assigned to genotype-guided arms, 116 underwent *CYP2C19* testing and 378 were tested for *CYP2D6* ($n = 25$ participants received both). The median TAT for *CYP2C19* ranged from 3 to 11 days and from 8 to 10 days for *CYP2D6*. *CYP2D6* TAT was approximately 2 days longer when the samples had to be sent in from partner sites versus collection at UF Health (Table 2). Although prescribers did not express challenges related to TAT, we believe it was a challenge in that the results were not available at the point of prescribing, leading to delayed clinical action, as described later.

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Prescriber education strategies—We anticipated prescribers would have a pharmacogenetics knowledge gap based on current literature[2,35] and addressed this through multiple educational strategies. Pretrial prescriber education included one hour of content delivered at formal grand rounds presentations; via on-demand, web-based presentations; during in-office prescriber lunch meetings; or at clinical in-services (protocol review only). All educational programs were associated with continuing medical education (CME) credit and offered prescribers the opportunity to participate in their own personal genotyping.[36] A series of postimplementation interdisciplinary case conferences was held at the prescribers' request for the *CYP2D6*/*CYP2C19*-SSRI trial.

Formal grand rounds presentations reached the largest number of prescribers (attendance of approximately 50 prescribers per educational session across two presentations). Of the 20 prescribers given access to the on-demand web-based education for their trial, 4 (20%) completed it, suggesting that offering online CME is not enough incentive to complete education. In-person prescriber education was offered over lunch to four prescribers, with 100% participation. This appears to be an alternative to grand round presentations to address educational gaps. Twenty-seven percent of prescribers (17 of 64) underwent personal genotyping as part of the educational process, with 100% of these individuals reporting this was beneficial in the educational process. A solution to increase uptake is to collect samples at a face-to-face educational program.

During the post-trial teleconference with providers, prescribers expressed that patient-centered, case-based educational programs were essential to clinical adoption. Patient case conferences and/or discussions conducted for prescribers were particularly effective in facilitating prescriber education and adoption of drug therapy recommendations.

Pharmacogenetic results—Phenotype frequencies for both CYP2C19 and CYP2D6 were as expected for each trial based on population frequencies (Table S3). *CYP2D6* results were unable to be determined in 4 of 378 participants, even with repeated testing. *CYP2C19* testing had zero undetermined results. Although individual-level data were not available, based on health system percentages, 12% of buccal samples had to be repeated at least twice to obtain a *CYP2D6* result. Of those that were repeated, 3% had to be recollected as they failed to give a result after multiple attempts. In contrast, no *CYP2C19* samples had to be recollected. This suggests that blood samples may decrease the genotyping failure rate, and the need for sample recollection and repeat testing or results being reported as undetermined.

The pharmacogenetic lab report provides both genotype and phenotype (based on genotype alone). This method of phenotype assignment does not factor in concomitant interacting medications, which are especially important in determining CYP2D6 phenotype. Our solution was to further interpret the phenotype provided from the lab report to account for phenoconversion. Of the participants tested for *CYP2D6*, 43 were taking a medication classified as a strong inhibitor, and 44 were taking a medication classified as a moderate inhibitor; 5 participants were taking both a moderate and strong inhibitor.[18] Overall, this resulted in phenoconversion for 83 of 378 (22%) participants tested for *CYP2D6* due to an interacting drug; most cases (77 of 83) changed a participant's phenotype from normal to

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actionable, while the remaining were from intermediate to poor. Accounting for phenoconversion resulted in more participants with an actionable phenotype, specifically in the *CYP2D6*-opioid trial at UF Health, where it increased from 17% to 44% of total participants. This suggests that considering CYP inhibitors is important for individualizing patient care.

Return of results, prescriber communication, and clinical actions— Pharmacogenetic test results were delivered to the prescriber in the EHR for 4 of the 6 trials (Table 3). Prescribers in other trials received results for all participants directly via fax or email, which were then uploaded into the EHR as a scanned PDF document. Of the trials in which pharmacogenetic results populated in the EHR, the UF Health study sites (n = 3)returned the result as a discrete field, which allowed for creation of active clinical decision support alerts (e.g., Best Practice Advisories [BPAs]). Two of these trials (*CYP2D6/CYP2C19*-SSRIs and *CYP2D6*-opioids at UF Health) opted to build BPAs (either before or during implementation), which fired if pharmacogenetic results were available, actionable, and the target drug was ordered (Fig. 1). Actionable phenotypes are defined with the associated clinical recommendations and delivery summarized in Table 3. Pharmacist consults, where indicated, were uploaded into the EHR within two weeks of genotype results; additional detail previously published.[20,21] Prescribers provided anecdotal feedback that they placed a high value on pharmacist consultation and BPAs for interpreting and integrating pharmacogenetic results, suggesting that that clear, concise guidance provided through active alerts or pharmacists' consults is important to prescribers and facilitated their workflow.

Waiting for genotype results presented a challenge for prescribers to determine when to use them (e.g., interpret and apply results at the next face-to-face patient encounter, or change patient's medication if warranted at the time the test result was returned). In three of the four adult trials, no action was taken until the next visit, and the adherence to genotype-guided recommendations was low (Table 3). It was also low in the *CYP2D6*-opioid cancer pain trial, where the predominant drug in question was oxycodone and prescribers may have been hesitant to change therapy if pain seemed well controlled. In contrast, for the trials in children, the prescribers and parents were often willing to await the results for drug initiation or therapy change, and adherence to genotype-guided recommendations was 87% and 100%, respectively. In the *CYP2C19*-PPI trial at Nemours, the genotype result in some clinics was available the same day to be acted on. In the *CYP2D6/CYP2C19*-SSRI trial, appointments were scheduled for 2 weeks following the genotyping order so that genotype-guided prescribing could be done at that time. This suggests that the difference in adherence to the recommendations was due to a greater focus on initiating the most appropriate therapy in children and willingness for prescribers and parents to wait until genotype results were available, even if it meant scheduling another appointment soon afterward. On the other hand, for adults, it is possible that waiting until the next visit (which may have been months after results were returned) resulted in some prescribers not considering the genotype-guided recommendation provided. A solution to optimize the prescriber's ability to act on genotype results and avoid disrupting workflow is to have it available during the patient encounter. Almost all the participants in the control arms who were offered genotyping (n = 247)

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elected to be genotyped (90%). A review of the post-trial period (3 months) for the *CYP2C19*-PPI trial at UF Health (i.e., after control participant's pharmacogenetic test resulted) indicated that medication changes aligning with the control participant's actionable phenotype occurred. There were nine changes in total, which was an equal number of changes made during the trial period for participants in the genotype-guided arm. This suggests that both patients and providers value the pharmacogenetic results, and they were useful after the study was completed. However, this 3-month follow-up duration might not be long enough to capture all genotype-guided medication changes. For example, in the *CYP2C19*-PPI trial at UF Health, only 34% (21 of 61) of participants in the genotype-guided arm had a face-to-face encounter with their prescriber after the genotype result was available and before the end of the three-month study period. This suggests that more medication changes may occur once the patient follows up with their prescriber.

During the post-trial teleconference, prescribers reported that they could not recall all their patients who had been genotyped and anticipated this challenge to persist in the future. The solution during the trials was to make note of ordering the test in the plan portion of their encounter note, allowing for proper follow-up. However, this is a short-term solution. Additionally, some prescribers expressed concerns about locating and interpreting results, instead preferring automated alerts to tell them exactly what to do. A future solution, in addition to BPAs, is to have a section of the patient's chart dedicated to pharmacogenetic results and interpretations, ideally making existing results discoverable upon quick glance.

DISCUSSION

We have successfully implemented pharmacogenetic testing into practice; successful to the extent that prescribers are willing to order genotype tests, participants are willing to be tested, genotype TAT is reasonable, medication changes were made that aligned with phenotype, and genotype tests remain clinically available. In doing so, we identified 11 challenges and learned lessons across six different pharmacogenetic implementations that will guide future efforts (summarized in Table 4). These lessons provide insight for others initiating similar clinical pharmacogenetic implementations.

Significant challenges were related to identifying optimal sample collection methods, waiting for genotype results, collecting sufficient participant feedback via questionnaires in pragmatic trials conducted in busy clinical settings, educating prescribers, and developing clinical recommendations that integrated pharmacogenetic test results and concomitant drug therapies.

Numerous potential solutions to these challenges were identified through comparison of strategies used across different trials. For example, taking extra steps to ensure noninvasive sample collection (e.g., buccal) for genotyping in children was beneficial and associated with higher enrollment rates. Others have also found that blood draws are a barrier to children participating in pharmacogenetic testing, and similarly now offer buccal tests.[6] Buccal tests are also more convenient for all patients, as not all clinics have phlebotomy stations; however, this must be balanced with the possibility that blood samples may not require recollection as often as buccal. While some prescribers and participants appeared to

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be willing to wait for a drug therapy decision until genotype results were available, having the result available at the patient encounter would optimize the prescriber's ability to act upon it. One potential reason for lower adoption of genotype-guided medication changes in adults may be that patients did not return to their prescriber in the 3-month study period. Treating pharmacogenetic test results like another lab result appeared to work well in prescribers' workflow for treating adults and it will be interesting to follow up on use of pharmacogenetic results post-trial.

Regarding patient questionnaires, strategies that limited the number of times survey completion was required helped improve patient completion rates. Specifically, trials that administered questionnaires at two time points were associated with the highest completion rates. It is difficult to determine if an association exists between use of pharmacogenetic testing and PROs if there are limited responses to work with. Although there is no hard cutoff, a response rate of 50–60% or greater is optimal to avoid inaccurate conclusions.[37]

Methods to overcome prescribers' knowledge gaps in pharmacogenetics were considered during trial design based on evidence that a large proportion of health-care providers lack confidence in using and applying pharmacogenetic test results in normal patient care.[2,35] We used multiple strategies but found that fostering ongoing relationships between the clinical prescribers and the PMP team with regular case conferences increased the likelihood that providers would act on results, suggesting this approach was most likely to increase prescriber comfort with interpreting pharmacogenetic results. Explicitly, the only trial that had a drug therapy recommendation acceptance rate of 100% employed patient case conferences for prescribers. Further, prescribers who received personal genotyping reported a positive learning experience. Others have also implemented this approach, and the prescribers reported increased comfort.[38] Personal genotyping is one approach we continue to use at UF Health to overcome barriers to prescribers' comfort level and facilitate engagement in ordering pharmacogenetic tests.

Some potential solutions to challenges were identified specifically by prescribers engaged in the study during implementation and data collection. For example, while interpreting pharmacogenetic results was a challenge for some, providers were able to utilize pharmacist consult notes. Consults and active alerts were discussed in great detail on the teleconference, and all prescribers came to consensus that the guidance must be clear and concise to allow prescribers to quickly and easily digest the information. This aligns with other studies in which providers have expressed a preference for precise, patient-specific guidance in the EHR on how to use pharmacogenetic data in patient care.[6,38,39] When clinical decision support alerts are employed, prescriber input and review are essential to improve communication and clarity and minimize "alert fatigue."[7,39] Within the UF Health PMP, a champion prescriber for each implementation was engaged in the alert development and approval process.

While we believe normal metabolizers are clinically informative, we do not currently fire BPAs for them in an effort to reduce "alert fatigue." It is crucial to remember that normal metabolizers may phenoconvert into an actionable phenotype, and in lieu of advanced clinical decision support that considers concomitant medications, we were only able to

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provide the calculated phenotype when pharmacists' consults were provided. Phenoconversion appears to be of particular importance in adults with pain and most prescribers were not previously aware of the significant drug interactions caused by inhibitors. Adults, as compared with children, are typically prescribed more medications, which increases the likelihood to be prescribed an interacting drug. Further, patients with pain are often taking an antidepressant, which make up 35% of CYP2D6 inhibitors.[18] Phenoconversion can be complex, and this is yet another reason why clear and concise guidance should be provided to prescribers.

One common challenge that would be anticipated with solely clinical pharmacogenetic implementation, as opposed to a research pragmatic trial, is test reimbursement.[40] Our implementations utilized grant funding, which provided a controlled environment where we could focus on overcoming other known challenges and barriers. We recognize that variable reimbursement rates are a major barrier to wide-spread pharmacogenetic implementation, and current trials are exploring strategies to overcome this barrier.

In conclusion, the challenges we identified are similar to challenges others can expect to face when initiating a new pharmacogenetic clinical trial or clinical service. By disseminating solutions and continuing to discuss lessons learned from these challenges, we will all be more successful in integrating pharmacogenetic testing into clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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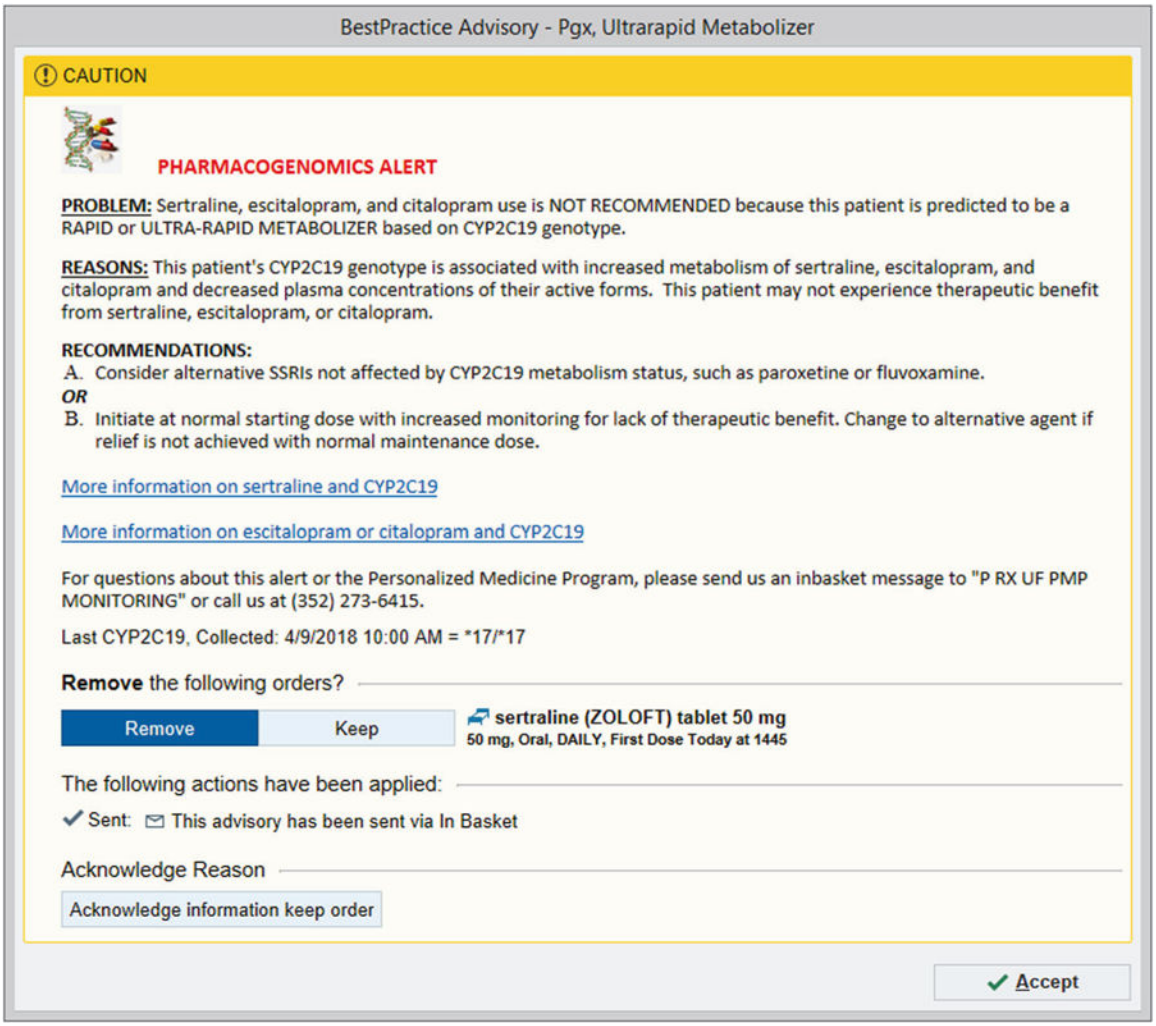

Fig. 1. Example of a *CYP2C19*-SSRI best practice advisory alert.

SSRI selective serotonin reuptake inhibitor.

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Table 1

Overview of clinical trials[20–34]

	***CYP2D6*-opioids**			***CYP2C19*-PPI**		***CYP2D6/CYP2C19*-SSRIs**
	OneFlorida Primary Care	**UF Health Primary Care**	**UF Health & Moffitt Specialty Clinics**	**UF Health Specialty Clinics**	**Nemours Children's Health Specialty Clinics**	**UF Health Specialty Clinics**
Number of participating clinics	2	7	2	1	3	1
Eligibility criteria[a]	Adults with chronic, noncancer pain		Adults with cancerassociated pain	Adults with GERD	Children with GERD	Children with depression, anxiety, or OCD
Total participants	104	371	86	123	60	49
Enrollment period	7/2015–4/2016	5/2015–6/2017	4/2016–4/2018	½017–7/2017	3/2017–8/2017	9/2016–½017
Study duration	12 weeks		8 weeks	12 weeks		12 weeks
Questionnaire(s) or tool used	Pain-CHOIR[b]		BPI-SF MDASI	GOS	SN-5	Side effects
					SafetyQ	CDI
				RDQ	PedsQL	SCARED
					GASP-Q	OCI-R
Total questions	70[b]		55	29	105	114
Weeks administered	0, 12		0,2,4,6,8	0,12	0–12[c]	0, 1, 2, 4, 8, 12

BPI-SF Brief Pain Inventory–Short Form, *CDI* Children's Depression Inventory, *CHOIR* Collaborative Health Outcomes Information Registry, *GASP-Q GERD* Assessment of Symptoms in Pediatrics Questionnaire, *GERD* gastro-esophageal reflux disease, *GOS* Global Overall Symptom Scale, *MDASI* M.D. Anderson Symptom Inventory, *OCD* obsessive compulsive disorder, *OCI-R* Obsessive Compulsive Inventory, *PedsQL* Pediatric Quality of Life Inventory, *PPI* proton pump inhibitor, *RDQ* Reflux Disease Questionnaire, SafetyQ Safety Questionnaire, *SCARED* Screen for Child Anxiety Related Emotional Disorders, *SN-5* Pediatric Sinonasal Symptom Survey, *SSRI* selective serotonin reuptake inhibitor.

[a]Detailed eligibility criteria are available elsewhere (clinicaltrials.gov: , , , and .[20–22]

[b]The pain-CHOIR tool used adaptive testing; we report the approximate average number answered.

[c]Except SN-5, which was administered at weeks 0, 4, 8, and 12.

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Table 2

Patient characteristics, genotype data, and questionnaire completion for those in the genotype-guided arm of each trial

	***CYP2D6* opioids**			***CYP2C19*-PPI**		***CYP2D6/CYP2C19*-SSRIs**
	OneFlorida Primary Care	**UF Health Primary Care**	**UF Health & Moffitt Specialty Clinics**	**UF Health Specialty Clinics**	**Nemours Children's Health Specialty Clinics**	**UF Health Specialty Clinics**
TotA gmotyped	33	235	38	61	30	25
Age in years, mean ± SD	63 ± 11	58 ± 13	60 ± 10	54 ± 16	12 ± 4	14 ± 4
Female, *n* (%)	46 (58)	156 (66)	17(45)	42 (69)	17(57)	19 (76)
Caucasian, *n* (%)	76 (95)	133 (78)	32 (84)	46 (75)	20(67)	21 (34:
African American, *n* (%)	3(4)	41(18)	5(13)	12 (20)	3(10)	2(4)
Genotype test turnaround time, days median (IQR)						
CYP2D6	10 (3 15)	8(7, 13)	10(8, 16 5)			8(7, 10)
CYP2C19				3(1. 4)	11 (8, 14)[a]	8(5.13)
Participants who had CYP2D6 phenoconversion, *n* (%)	9(11)	69(29)	4 (11)	-	-	1(4)
Percent of questionnaires completed by participants	98%	96%	57%	96%	44%	70%

IM intermediate metabolizer, *IQR* interquartile range, *NM* normal metabolizer, *PM* poor metabolizer, *PPI* proton pump inhibitor, *RM* rapid metabolizer, *SSRI* selective serotonin reuptake inhibitor, *UF* University of Florida, *UM* ultrarapid metabolizer

[a]For laboratory developed test (*n* = 24), the rest were done with SpartanRx, which resulted the same day.

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Table 3

Return of results, prescriber communication, and clinical action

	***CYP2D6*-opioids**			***CYP2C19*-PPI**		***CYP2D6/CYP2C19*-SSRIs**
	OneFlorida Primary Care	**UF Health Primary Care**	**UF Health & Moffitt Specialty Clinics**	**UF Health Specialty Clinics**	**Nemours Children's Health Specialty Clinics**	**UF Health Specialty Clinics**
Total genotyped	80	235	38	61	30	25
Test results available to prescriber	Fax	EHR		EHR	Email	EHR
Actionable phenotypes	UM, range (i.e., NM-UM, IM-NM),[a] IM, PM			UM, RM, IM, PM		UM, PM for CYP2D6 and/or UM, RM, PM for CYP2C19
General drug therapy recommendations	Switch to non-CYP2D6 mediated opioid (e.g., morphine) or nonopioid analgesic, or if reasonable (and relevant) discontinue CYP2D6 inhibitor			*50–100% Dose increase for UM/ RM25–50% dose decrease for IM/PM*	100% dose increase for UM, 50% dose increase for RM, 50% dose decrease for IM/PM	Avoid SSRI that is metabolized by the CYP enzyme that is actionable; use fluoxetine if actionable phenotype in both CYP2D6/ CYP2C19
Method for recommendation communication to prescriber	General information sheet	Patientspecific consults provided	Patient-specific consults provided and information sheet	Consults upon request[c] and general information sheet	Research coordinator communicated protocol recommendation	Patient-specific consults provided
Participants with an actionable phenotype,[b] *n* (%)	19 (24)	104 (44)	12 (32)	33 (54)	15 (50)	12 (48)[d]
Participants with an actionable phenotype who had a medication change that aligned with phenotype, *n* (%)	1 (5)	23 (22)	2 (17)	9 (27)	13 (87)	11 (100)[e]
When genotype results are used typically (for the majority)				Next visit	[f]Once resulted	Appointment at week 2 of study[f]

EHR electronic health record, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *PPI* proton pump inhibitor, *RM* rapid metabolizer, *SSRI* selective serotonin reuptake inhibitor, *UF* University of Florida, *UM* ultrarapid metabolizer.

[a]When copy-number variation was present, it sometimes resulted as a range phenotype because the copy-number variation could not be detected for specific alleles.

[b]Phenotype accounts for phenoconversion.

[c]Zero consults requested.

[d]Participants only counted once, participants with at least one gene with a phenotype warranting a recommendation.

[e]11 of 11, as one individual had a phenotype that was considered actionable, but did not start an SSRI. Three individuals continued their SSRI that was metabolized by an actionable CYP enzyme, but had dose increases and thus counted as aligning with phenotype.

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[f] Appointments were scheduled at week two of the study to allow for genotype results to be acted upon.

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Table 4

Summary of challenges and potential solutions

Challenge		Potential solution/lesson learned
Trial design	Randomization	• Randomizing at the patient level provides more similar baseline characteristics between comparison groups versus randomization by enrollment site (e.g., cluster randomization)
	Questionnaire completion	• Patients are willing to complete questionnaires so long as they are not overly burdensome or too frequent • To assess association between outcome and use of pharmacogenetics, the majority of questionnaires need to be completed, and a high percentage of patients with actionable phenotype need to have drug changed
Provider education	Prescriber knowledge gaps	• Prescribers learn best from case-based education; providing this type of education upfront as well case discussion sessions throughout is ideal • Having prescribers undergo personal genotyping is a beneficial educational method • Offering online CME is not enough incentive to complete education • In-person education methods (e.g., noon conference/grand rounds) are well attended
Test order and interpretation	Identifying who to test	• Prescribers would like electronic decision support tools to identify potentially appropriate patients to test
process	Children do not like blood draws	• Offering noninvasive genetic sample collections is key for younger populations • Blood draws do not seem problematic in adults, however may not be the most convenient option as not all clinic locations have phlebotomy stations
	Turnaround time for pharmacogenetic test results	• Genotype should be available during patient encounters to optimize prescriber's ability to act on it • Prescribers, patients, and parents are willing to wait for results for drug therapy decisions in some settings
	Phenotypes resulting as a range or indeterminate	• Having a testing platform that can detect which CYP2D6 allele is duplicated is ideal • Blood samples may result in fewer undetermined phenotypes as compared with buccal samples
	Phenotype results	• Normal metabolizers, although not a classic "actionable" phenotype, are clinically informative • Concomitant medications (e.g., CYP2D6 inhibitors) must be considered to evaluate true phenotype, especially in patients who are genotypically normal metabolizers
	Prescriber interpretation and integration of pharmacogenetic results	• Prescribers highly depend on consults from pharmacists • Clear concise guidance must be provided through active alerts or consults in the EHR • Prescribers value eventual availability of pharmacogenetic results for their patients enrolled in control arms[a] • Genotype data availability at the time of prescriber–patient encounter, and clarity for clinician of availability of the genotype data and recommended actions is likely important for high levels of adherence to genotype-guided recommendations
EHR integration	Prescribers cannot recall every patient who was genotyped	• Prescribers do not necessarily look in the chart for pharmacogenetic results, especially if they are buried with other lab results ○ An ideal solution is a section of the patient's chart for genetic results, and a quick indicator to note if there are results in there ○ A workaround is ensuring the prescriber notes in their encounter note that they are ordering a pharmacogenetic test; then, they will review prior to patient's next visit and will know to look for results • Prescribers want alerts to tell them exactly what to do if results are available
Patient perceptions	Patient perceptions and knowledge of pharmacogenetics	• Patient education to manage patient expectations on what information pharmacogenetic results will provide is essential • Having brief patient-friendly educational materials for before and after testing is ideal • Patients value receiving pharmacogenetic results at the end of the study

CME continuing medical education, *EHR* electronic health record.

[a]All but the *CYP2D6*-opioid cancer pain trial offered control participants pharmacogenetic testing.