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ARTICLE

Implementing a pragmatic clinical trial to tailor opioids for chronic pain on behalf of the IGNITE ADOPT PGx investigators

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Abstract

Chronic pain is a prevalent condition with enormous economic burden. Opioids such as tramadol, codeine, and hydrocodone are commonly used to treat chronic pain; these drugs are activated to more potent opioid receptor agonists by the hepatic CYP2D6 enzyme. Results from clinical studies and mechanistic understandings suggest that CYP2D6-guided therapy will improve pain control and reduce adverse drug events. However, CYP2D6 is rarely used in clinical practice due in part to the demand for additional clinical trial evidence. Thus, we designed the ADOPT-PGx (A Depression and Opioid Pragmatic Trial in Pharmacogenetics) chronic pain study, a multicenter, pragmatic, randomized controlled clinical trial, to assess the effect of *CYP2D6* testing on pain management. The study enrolled 1048 participants who are taking or being considered for treatment with CYP2D6-impacted opioids for their chronic pain. Participants were randomized to receive immediate or delayed (by 6 months) genotyping of *CYP2D6* with clinical decision support (CDS). CDS encouraged the providers to follow the CYP2D6-guided trial

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recommendations. The primary study outcome is the 3-month absolute change in the composite pain intensity score assessed using Patient-Reported Outcomes Measurement Information System (PROMIS) measures. Follow-up will be completed in July 2024. Herein, we describe the design of this trial along with challenges encountered during enrollment.

Study highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Several opioids are activated by CYP2D6 to more active metabolites. Prior research suggests that using the CYP2D6 status may improve pain control and reduce the side effects in patients taking opioids. However, there are limited prospective randomized CYP2D6-guided clinical trials that evaluate CYP2D6 interventions.

WHAT QUESTION DID THIS STUDY ADDRESS?

Does the prospective utilization of *CYP2D6* genotype and phenoconversion information improve pain control and reduce side effects in patients currently taking or planning to take opioid therapy for chronic pain?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This manuscript describes the design of the ADOPT-PGx Chronic Pain clinical trial that will assess the impact of the CYP2D6-guided therapy in patients with chronic pain.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The results of this study are expected to help determine whether the CYP2D6 status of patients should be used to guide the clinical strategies to treat chronic pain.

INTRODUCTION

Chronic pain is a common symptom that adversely affects quality of life and is associated with significant economic costs. According to a survey in the United States, an estimated 50 million adults (~20% of adults) feel pain most or every day.[1] Estimates of the number of people living with back pain range from 7% to 30%[2,3] and chronic pain is a leading cause of disabilities.[4] Back pain results in an approximately 15 million physician office visits annually in the United States.[5] It is one of the most common symptoms reported among patients in primary care and is a major contributor to disability.[5,6] Chronic pain is frequently treated with opioids, despite risks of dependence, overdose, and diversion.[6] Although opioids are frequently tolerated and effective, there is substantial interindividual variability in the analgesic response, in part due to variability in the cytochrome P450 2D6 (*CYP2D6*) gene.[7–10] Commonly prescribed opioids, such as hydrocodone, tramadol, and codeine, have relatively low or absent analgesic properties, but they are O-demethylated to more pharmacologically active metabolites by the liver enzyme, CYP2D6.[8] Consequently, patients who inherit genetic variants in *CYP2D6* that result in CYP2D6 intermediate or poor metabolizer phenotypes have partial or complete loss of CYP2D6 enzymatic activity, respectively, and are at risk of inadequate analgesia.[8] Conversely, those who inherit the CYP2D6 ultra-rapid metabolizer phenotype are at risk for opioid toxicity.[8] In addition, a number of commonly used drugs are potent inhibitors of the CYP2D6 enzyme, and they can also impact the bioactivation of these opioids. Indeed, a recent study documented that approximately 20% of patients with chronic pain treated with an opioid are also taking a concomitant CYP2D6 inhibitor.[11] Concurrent use of these CYP2D6 inhibiting medications can also impact the opioid response by converting these individuals to phenotypic intermediate or poor CYP2D6 metabolizers.

Research suggests that *CYP2D6* pharmacogenetic data can help clinicians when prescribing opioids. Accordingly, the Clinical Pharmacogenetics Implementation Consortium (CPIC),[12] the Dutch Pharmacogenomic Working Group (DPWG),[13,14] and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS)[15] have each published *CYP2D6*-opioid guidelines that provide recommendations for using *CYP2D6* genetic results when prescribing opioids. A recent single-site pragmatic clinical trial that considered CYP2D6 phenotype (including both *CYP2D6* genotype and concurrent use of CYP2D6 inhibitor drugs) demonstrated

that CYP2D6-guided pain management improved pain control (composite pain intensity) compared with usual care (without *CYP2D6* testing).[11] Although CPIC, DPWG, CPNDS, and various lines of evidence support *CYP2D6* genotype-guided use of opioid analgesics, *CYP2D6* genotyping is rarely implemented in clinical practice.[16] This is due, in part, to the demand for additional evidence demonstrating CYP2D6-guided opioid therapy can improve pain control or reduce opiate-related adverse effects. Herein, we describe a pragmatic, randomized, controlled clinical trial designed to fulfill that need. We will evaluate the impact of genotype-guided opioid therapy on pain control. The results of this trial should help clarify the utility of CYP2D6 phenotype (defined by *CYP2D6* genotype and drug–drug interactions) to guide opioid therapy, which may provide compelling evidence necessary to drive implementation into clinical practice.

METHODS

The IGNITE PTN and ADOPT-PGx

The Implementing Genomics into Practice Pragmatic Trials Network (IGNITE PTN) was established to determine the clinical utility and cost-effectiveness of genomic medicine interventions, assess approaches for real-world application of genomic medicine in diverse clinical settings, and produce generalizable knowledge on clinical trials using genomic interventions.[17] The National Human Genome Research Institute (NHGRI) of the National Institutes of Health both funds and helps lead the network. The IGNITE PTN Coordinating Center at Duke University provides a central resource for trial coordination, design support, and oversight. The network is focused on including participants from diverse backgrounds, including underrepresented minorities and participants from medically underserved areas and populations.

The IGNITE PTN has implemented "A Depression and Opioid Pragmatic Trial in Pharmacogenetics," or ADOPT-PGx (ClinicalTrials.gov NCT04445792).[17] ADOPT-PGx is composed of three individually powered pragmatic, randomized trials testing the efficacy of genotype-guided therapies to treat depression and pain. The study designs of the ADOPT-PGx pragmatic trials focused on acute pain and depression have previously been described,[18,19] and the chronic pain study is described in this article.

Chronic pain trial design

Figure 1 depicts an overview of this clinical trial's design. Enrolled individuals with chronic pain were randomized to immediate (intervention arm) versus delayed (at 6 months; control arm) *CYP2D6* genotyping with consideration of CYP2D6 drug interactions to define a CYP2D6 phenotype, to guide recommendations for the patient's prescriber. Genotyping for *CYP2D6* functional genetic variants was performed at Clinical Laboratory Improvement Amendment (CLIA) accredited laboratories at enrollment for participants randomized to the intervention arm and after the 6-month survey for participants randomized to the control arm, indicating participants completed the trial. Consistent with the pragmatic nature of the trial, the participants' providers were free to use the CYP2D6 recommendations as they deemed clinically appropriate. The primary analysis is a modified intention-to-treat (mITT) analysis of pain control at 3 months defined as the absolute change in the composite pain intensity score (defined in the outcomes section below) from baseline to 3 months in participants who are genetically or pheno-converted CYP2D6 intermediate metabolizers (IM) or poor metabolizers (PM).

IRB approval

The Duke University IRB approved all aspects of this study, serving as the single IRB. All other sites agreed to rely on the Duke University central IRB. All patients provided written informed consent.

Trial recruitment sites

Participating trial sites include Duke University Health System, Eskenazi Health, Indiana University Health, Institute for Family Health at Mount Sinai Health System, Meharry Medical College, Mount Sinai Health System, Sanford Health, University of Florida Health in Gainesville and Jacksonville, and Vanderbilt University Medical Center.[17,18] Prior to enrollment, investigators and staff at the individual sites discussed the study and recruitment with primary care and pain-relevant specialty clinic leaders and clinicians. Provider education strategies for each clinical site are shown in Table 1.

Inclusion criteria

Individuals were eligible for inclusion in the study if they met all of the following inclusion criteria: (1) age ≥ 18 years, (2) English speaking; some sites were also approved to enroll Spanish-speaking participants, (3) had a visit to a primary care clinic or pain-relevant specialty clinic at the

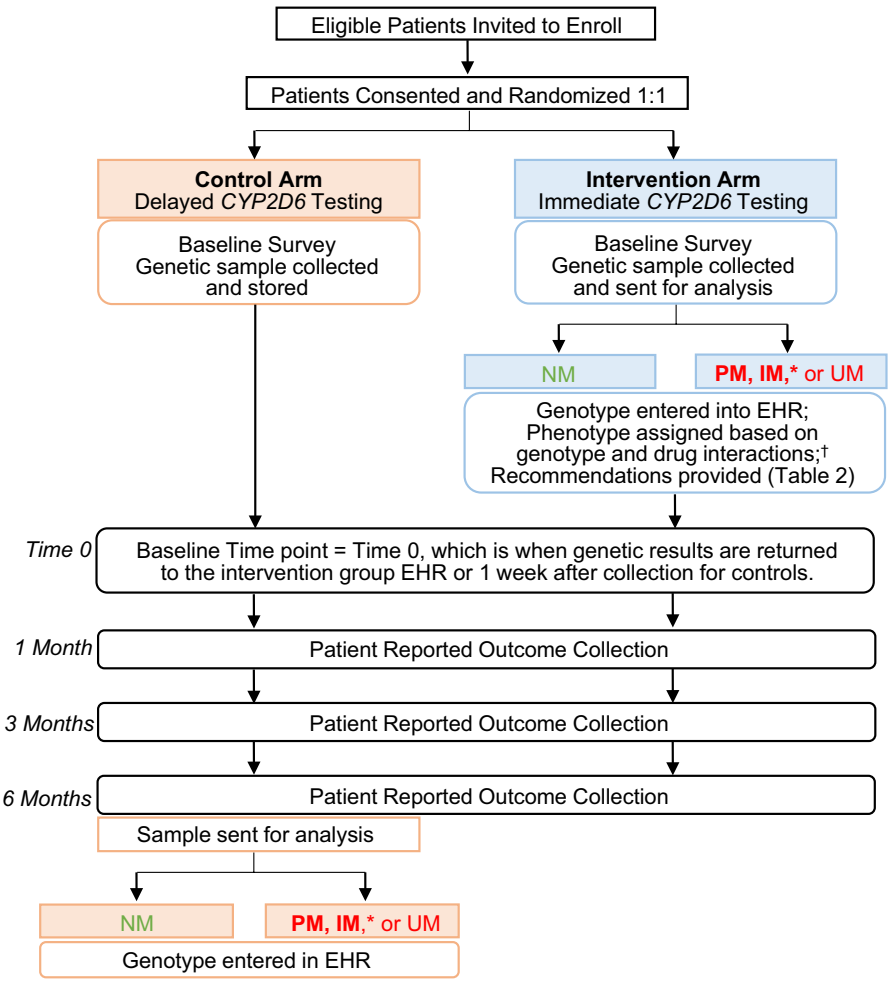

FIGURE 1 Overall trial scheme. Time 0 for the intervention arm is when the results are returned to the electronic health records and 1 week after the sample collection for the control arm. AS, CYP2D6 activity score; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer. *Intermediate metabolizer was defined as CYP2D6 activity score >0 and ≤0.75. Parts of this figure are similar or the same as those in the following manuscript with permission from the publisher and authors.[18]

enrolling site's healthcare systems, (4) history of pain for at least the last 3 months, and (5) currently being treated or being considered for treatment with tramadol, hydrocodone, or codeine to improve pain management.

Exclusion criteria

Individuals were excluded if they met any of the following exclusion criteria: (1) life expectancy less than 12 months, (2) unable to provide informed consent and/or to complete the study protocol due to cognitive impairment, (3) currently institutionalized (e.g., mental health, nursing home, or prison), (4) too ill to participate, (5) history of allogeneic stem cell transplant or liver transplant, (6) those with prior clinical *CYP2D6* pharmacogenetic test results, (7) previously enrolled in one of the other ADOPT PGx trials, (8) plan to move out of the area within 6 months of enrollment, (9) undergoing treatment for an active cancer diagnosis, (10) currently taking daily opioids other than tramadol, codeine or hydrocodone for treatment of pain, or (11) currently using a pain pump.

Enrollment, informed consent, and randomization

A national committee of patient, advocate, and clinician stakeholders, and groups of similar stakeholders at many local sites co-developed materials and strategies used to engage patients and helped address recruitment challenges that arose throughout the study. A variety of approaches were utilized to identify patients being seen in the target clinics who were potentially eligible for participation. Research coordinators called, or approached in clinic, individuals who met eligibility criteria based on electronic health record (EHR) review. Trained clinical research coordinators obtained informed consent, either in-person or remotely via e-consent, from willing individuals who met all eligibility criteria. Individuals who provided informed consent were randomized (1:1 allocation) to the immediate genotyping (intervention) or the delayed genotyping (control) arm. Randomization was stratified by enrollment site and the presence/absence of depression with random block sizes generated by a statistician at the coordinating center. The stratification by depression

TABLE 1 Clinical site clinical decision support (CDS) and provider education comparison.

	UF Health	Nemours Children's Health	Mount Sinai	IFH	VUMC	Sanford Health	MMG + NGH	DUHS	IU Health	Eskenazi Health
Clinical decision support										
Automated alerts based on opioid Rx + PGx	X	X			X	X		X	X	X
Automated alerts based on opioid Rx + CYP2D6 inhibitor + PGx			X[a]	X[a]						
Consult note placed based on CYP2D6 inhibitors + PGx	X	X			X	X	X	X	X	X
Provider education strategy										
Presentations in person or via videoconference prior to enrollment	X	X	X	X	X	X		X	X	X
One-on-one or small group meetings		X	X	X	X	X	X			
Emails		X	X	X	X	X	X			
Refresher presentations periodically after trial launch								X		
Laminated cards of enrollment criteria and how to refer patients into the trial for posting at work stations								X		

Note: Parts of this table are similar or the same as that in the following manuscript with permission from the publisher and authors.[18]

Abbreviations: DUHS, Duke University Health System; IFH, Institute for Family Health at Mount Sinai Health System; IU, Indiana University; MMG, Meharry Medical Group; MSHS, Mount Sinai Health System; NGH, Nashville General Hospital; PGx, pharmacogenetics; Rx, prescription; UF, University of Florida; VUMC, Vanderbilt University Medical Center.

[a]Recommendations are provided solely through automated alerts because of insufficient pharmacy support to provide consult notes.

was included because of the close relationship between depression and chronic pain.

Sample collection and genotyping

After enrollment and randomization, biospecimens were collected for genotyping. All sites accepted blood samples (venipuncture), and some also offered genotyping from either buccal swabs or saliva. The options for each site depended on the laboratory-developed tests that were available at the CLIA-certified testing laboratories used by each site. Research coordinators ensured that the collected samples were sent for pharmacogenetic testing.

Pharmacogenetic testing for *CYP2D6* was conducted at one of six laboratories across the participating trial sites.[18] The minimum list of required *CYP2D6* alleles to test is shown in Figure 2; this includes the *CYP2D6* copy number to identify *CYP2D6*5* alleles and those with >2 copies of *CYP2D6*. In those with >2 copies, laboratories were not able determine which allele was copied, and they were required only to determine whether there were more than two copies but not how many more than two; this is currently the standard for clinical *CYP2D6* genetic testing. CYP2D6 activity scores and phenotypes predicted from the *CYP2D6* genotypes were determined as previously reported and are shown in Figure 2.[18] CYP2D6 phenotypes include PM, IM, normal metabolizers (NM), ultra-rapid metabolizers (UM), and indeterminant. The metabolizer status was also modified for participants concurrently taking medications that are defined by the FDA as strong or moderate CYP2D6 inhibitors commonly taken by these patients, as shown in Figure 2 and based on the rationale previously described.[20–23] We did not include weak inhibitors as we expected them to have minimal impact on opioid efficacy. The calculation and use of the CYP2D6 activity scores are the same as described for the ADOPT-PGx acute pain trial.[18] Intermediate metabolizers were defined as CYP2D6 activity scores of >0, but ≤0.75, to be consistent with the previous pilot study.[11] Additional secondary analyses will also be conducted to determine whether the revised CPIC designations for some *CYP2D6* alleles or the

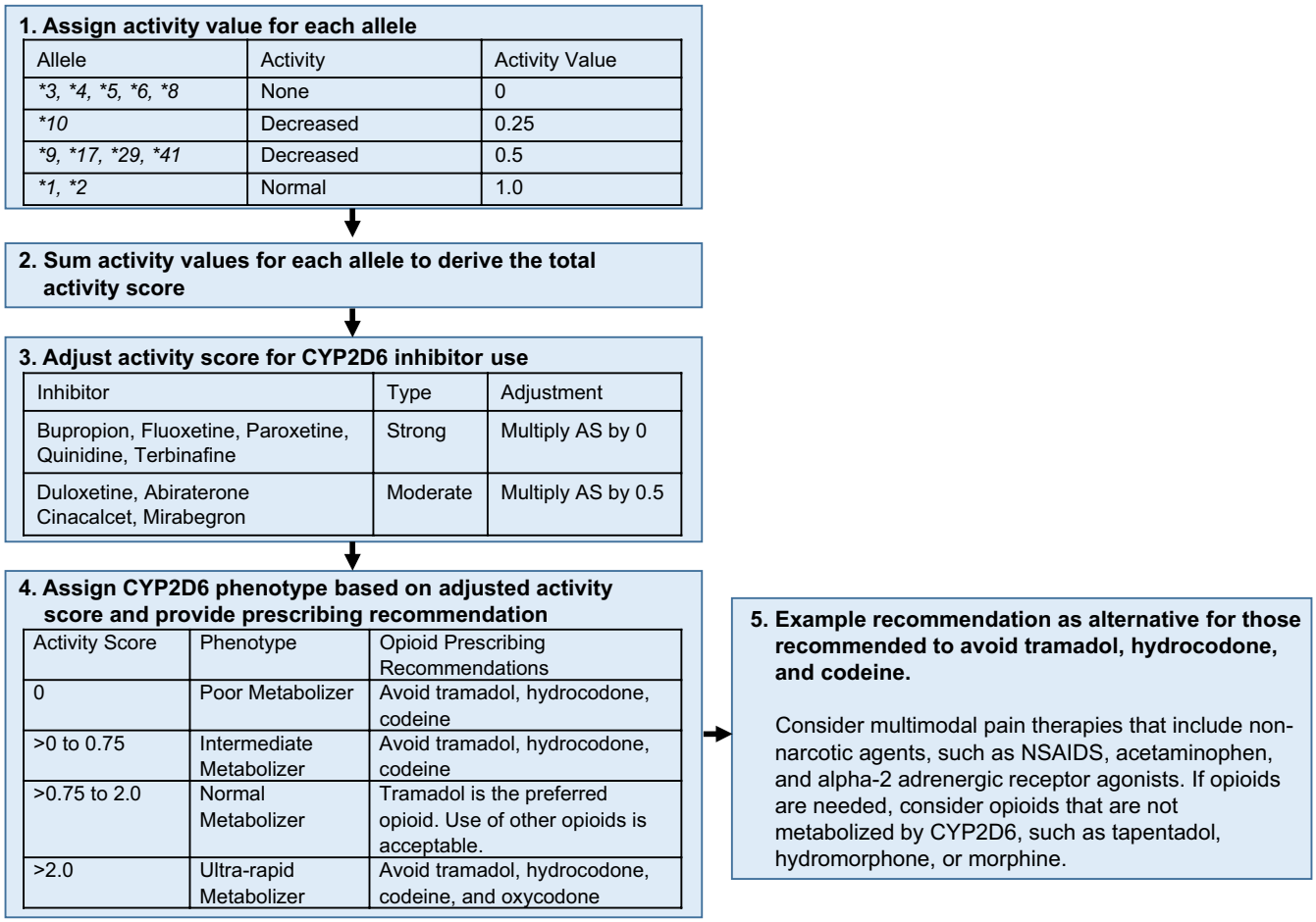

FIGURE 2 Clinical recommendations for pain medication use in participants with each CYP2D6 metabolizer status based on genetics and with the CYP2D6 inhibitor adjustments. Parts of this figure are similar or the same as those in the following manuscript with permission from the publisher and authors.[18]

intermediate metabolizer activity score range up to 1.0 results in different outcomes. At some sites, the *CYP2D6* genotyping was conducted as part of a panel that included other genes that were reported into the EHR, but those additional genes were not used to guide the opioid therapies.

Intervention

The intervention consisted of immediate return of CYP2D6 metabolizer status, defined by pharmacogenetic testing results and relevant CYP2D6 inhibitor prescriptions, to the participant's healthcare provider and the EHR. For the delayed genotyping (control) group, laboratory processing and return of results were delayed for 6 months, after the study participant had completed data collection and their participation in the study.

Providers received CYP2D6 phenotype results based on standard laboratory processes at each site. Methods included transmission of discrete pharmacogenetic results to the EHR; supplementary clinician-friendly consult notes conveyed the significance of the actionable phenotype based on genotype results and CYP2D6 drug interactions (8 out of 10 sites; see example in Figure S1); and computerized clinical decision support (CDS) alerts integrated with the EHR (9 out of 10 sites) (see example in Figure 3). Providers were alerted to the CYP2D6 metabolizer status and related recommendations through CDS when ordering tramadol, codeine, or hydrocodone if the patient had a clinically actionable genotype in the EHR. Recommendations for each CYP2D6 activity score are described in Figure 2. For safety reasons, providers were also alerted to avoid oxycodone for CYP2D6 UM. The sites that used CDS alerts are shown in Table 1.[18] Clinicians were the final arbiters for all clinical decisions. Participants could access their genotyping results through the healthcare systems' patient portals at some sites, and participants were allowed to discuss their results with their providers.

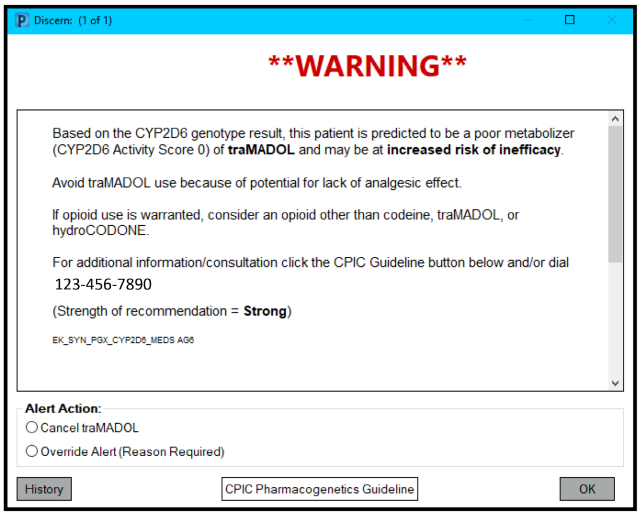

FIGURE 3 Example of a clinical decision support alert triggered by a tramadol prescription in a participant whose genotyping result revealed a CYP2D6 poor metabolizer.

Surveys and other outcome data

Follow-up surveys occurred at 1, 3, and 6 months following the baseline timepoint. These times were calculated relative to the time when the genotype results were returned to the EHR for the intervention arm and 1 week following the DNA sample collection for the control arm (Figure 1). At the designated times, baseline and follow-up surveys capture Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire data related to pain intensity scale, well-being and subdomains, prescription pain medication misuse scale, and emotional distress depression survey healthcare utilization, and questions related to productivity loss due to chronic pain, and opioid side effects. The surveys used included the PROMIS 43 v2.1 + Item Bank v1.0 Emotional Distress—Depression Short Form 8b, PROMIS pain intensity scale v 1.0, PROMIS prescription pain medication misuse scale v1.0–Short Form 7a, PROMIS emotional distress—depression 8b survey, and an opioid side effects survey. In addition, medication inventories were included in the baseline and 3-month surveys; they will be used to evaluate changes in medication from the baseline to the primary end-point time period (3 months).

The Coordinating Center implemented a data management system using REDCap[24] that captures survey data across study sites.[17] Research coordinators at each site collect the baseline surveys. Follow-up surveys were collected either via telephone or web-based methods by the University of Florida College of Pharmacy call center. The call center was blinded to which arm the participants were in. When the call center was unable to reach participants, local research coordinators were notified and also attempted to contact those participants and collect the data.

Healthcare utilization and economic analyses will be performed using Medicare or Medicaid claims data for patients covered by those entities. These data will be used to compare the healthcare costs between the control and intervention arms. Additionally, cost-utility analyses will be conducted to assess the cost-effectiveness of *CYP2D6* testing on pain management from a third-party payer perspective. Efficacy and utilities, including responses from the PROMIS-43 instrument, will be obtained from the clinical trial, while cost data will be assessed through claims data analysis. Healthcare utilization between the

arms will be compared using participant-reported data from the surveys alongside the claims data, examining outcomes such as emergency department visits, hospitalizations, and physician visits.

Outcomes

The primary study end point is the absolute change in composite pain intensity score (3-month pain score—baseline pain score) assessed using the PROMIS[25] pain intensity survey, from baseline to 3 months after genetic testing results were returned to the provider (or from 1 week after sample collection for the control arm). The 1 week after sample collection was chosen based on the estimation that it would take approximately 1 week to return the results for the intervention arm. Composite pain intensity was calculated as the mean of the current pain and worst and average pain intensity over the previous 7 days. The data collection instruments and timepoints at which data are collected from participants are shown in Table 2.

Secondary end points include (1) pain reduction magnitude (3 month composite pain intensity divided by baseline composite pain intensity, i.e., percent change) at 3 months, (2) proportion of participants achieving clinically significant pain reduction (30% reduction in composite pain intensity from baseline as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [IMMPACT] and others[26–28]) at 3 months, (3) overall well-being per the PROMIS-43[29] survey, which assesses pain interference, physical function, sleep disturbance, social role and activities functioning, fatigue, anxiety, and depression, at 1-, 3-, and 6-month follow-up, (4) subdomains of overall well-being: pain interference, physical function, sleep disturbance, social role and activities functioning, fatigue, anxiety, and depression at 1-, 3-, and 6-month follow-up, (5) concordance between metabolizer phenotype/trial recommendations and prescribed medication; this will include data on the provider adherence to the provider recommendations, and (6) prescription pain medication misuse at 3 and 6 months.

Statistical analysis plan and sample size

We will analyze study results using a mITT analysis, comparing the intervention participants with an actionable CYP2D6 phenotype to the control participants with an actionable phenotype defined as CYP2D6 intermediate or poor metabolizer (i.e., CYP2D6 activity score ≤0.75). End points will be compared between arms using a two-sided *t*-test or Mann–Whitney U-test, as appropriate. If an imbalance in baseline characteristics between trial arms is identified, covariate-adjusted sensitivity analyses using linear regression will be conducted.

A prior study of pharmacogenetic testing in a chronic pain population provided initial estimates of the anticipated effect size for the absolute change in composite pain scores (Cohen's $D = 0.43$).[11] Assuming a reduced effect size (Cohen's D of 0.40), 268 intermediate or PM (134 in each arm) are estimated to provide 90% power with a two-sided type 1 error rate of 0.049, to account for a single interim analysis. Additional assumptions include that 30% of the participants would be intermediate or PM (including those with CYP2D6 drug interactions), and 10% would drop out, be lost to follow-up, or have missing data. As the

TABLE 2 Data collection schedule.

Outcome	Data source/instrument	Baseline[a]	1 month ± 7 days after baseline (Time 0)	3 months ± 14 days after baseline (Time 0)	6 months ± 14 days after baseline (Time 0)
Pain intensity	PROMIS® Pain intensity scale	X	X	X	X
Medications	Patient survey	X		X	
Opioid use disorder	PROMIS® – Prescription pain medication misuse subscale	X		X	X
Depression symptoms	PROMIS® emotional distress depression 8b survey	X	X	X	X
Opioid side effects	Adapted medication side effect survey (SPACE) [44, 45]	X		X	X
Well-being	PROMIS® 43	X	X	X	X
Healthcare utilization	Patient survey	X	X	X	X
Productivity loss	Patient survey	X	X	X	X

Abbreviation: PROMIS®, Patient-Reported Outcomes Measurement Information Systems.

[a]Baseline surveys are administered at enrollment.

total sample size is dependent on the prevalence of the intermediate or poor metabolizer phenotypes, 906, 994, or 1233 participants were needed to be enrolled if 33%, 30%, or 24% have these phenotypes, respectively.

DSMB

NHGRI appointed an independent Data and Safety Monitoring Board (DSMB) that meets semi-annually and is responsible for patient safety, trial progress, and criteria for early study termination.[17] A DSMB charter and "Data and Safety Monitoring Plan" were developed in collaboration with the IGNITE PTN, Coordinating Center, NHGRI, and enacted by the DSMB.

RESULTS TO DATE

Enrollment timeline

The trial enrolled its first participant in February 2021 and its last participant in October 2023 with a total of 1048 participants from all sites combined. Follow-up was planned through July 2024. As the trial progressed, we monitored the available results (both arms combined) of the metabolizer statuses and ultimately enrolled 1048 subjects.

Challenges and lessons learned to date

The COVID-19 pandemic delayed the start of the study and created barriers to enrollment. Some sites completely shut down enrollment of these types of trials as their healthcare systems managed the pandemic. When they did resume enrollment, many providers and healthcare systems remained occupied with pandemic care, had less time to consider participating in clinical studies, and had limited space for clinical research due to social distancing restrictions. As a result, teams pivoted to contacting patients by telephone call. Telephone calls are generally believed to be less efficient because many individuals are less likely to answer the phone from callers they do not recognize. Also, patients seem more likely to agree to enroll when coordinators are in the clinics, because they recognize that the coordinators are part of the healthcare system. These in person interactions were constrained during the pandemic. As a result of the above, enrollment was slower than expected. However, despite those challenges posed by the pandemic, we showed that recruitment of diverse participants into pharmacogenetic studies, even during a pandemic, is feasible and should be the goal of many clinical trials.

Nation-wide efforts resulting from state policies to mitigate the opioid epidemic also made recruitment more difficult. In some states, increased requirements for provider training and documentation of opioid prescriptions, along with limitations on quantities of opioids that could be prescribed, led to decreases in the frequency and duration of opioid prescriptions. In some institutions, increasing recognition of the potential for pharmacogenetic effects as well as opioid diversion and/or addiction led to changes in standard practices and approaches to chronic pain. One of the insights we learned from enrolling patients during the era of efforts to reduce opioid use is that some of our study teams heard from some potential participants that perceived restrictions on opioid prescriptions made them unwilling to participate in a trial that they thought might impair their ability to continue to receive opioid therapy for chronic pain conditions.

Clinical decision support was utilized to help providers follow the CYP2D6-guided recommendation. This CDS was needed because most providers are not familiar enough with the CYP2D6-based opioid recommendations, and it is possible that they would not be aware that there were *CYP2D6* genetic results in the participant's records. Pharmacogenetic CDS development and deployment were coordinated across enrolling sites by providing the essential elements that needed to be included; however, some variability in the CDS implementation occurred (see Table 1). We learned that this was because deployment required significant investments in health information technology to use genomic results from the EHR, because there was variability in the EHR software used, and in institutional policies. Thus, pragmatic trials requiring CDS implementation need to be flexible in their strategies across different healthcare systems.

Clinical pharmacogenetic testing is required for the trial intervention. Not all sites have this testing available on site as *CYP2D6* testing is notoriously challenging due to the many genetic variants, the need to determine copy number variations, and the challenges avoiding the *CYP2D7* and *CYP2D8* pseudogenes that have very highly similar sequences.[30] Those sites without onsite *CYP2D6* genotyping sent their samples to one of the other sites for genotyping. In addition, during parts of the trial, saliva as an acceptable DNA source was discontinued at some sites due to commercial reagent changes that resulted in insufficient DNA yields to run the genotyping assays; when these low yields were identified, blood samples were collected from those participants, and that resulted in successful genotyping. In addition, one clinical testing laboratory closed during the trial and one stopped doing the required variant testing. This highlighted the need to have backup strategies for conducting the CLIA-based genetic testing, especially in states that have additional required regulatory certifications beyond those of most other states.

DISCUSSION

Chronic pain is a common symptom with many sources that is challenging to treat safely and effectively.[1,2,5,6] Opioids can ameliorate pain in many patients, but their use comes with several drawbacks. In some patients and for some types of pain, opioids do not effectively alleviate the pain. In others, opioids can cause serious and fatal adverse drug reactions and can lead to opioid misuse and addictions.[6] Because of these concerns, recent efforts, and policies, including new state laws, have sought to ensure opioid use is appropriate for a clinical indication and to avoid overuse. Evidence is mounting that pharmacogenetic testing may help determine which opioid regimens are safe and effective for individual patients.[12] Genetic variants that are most consistently associated with opioid response are those that impact the CYP2D6 enzyme function. The CYP2D6 enzyme is expressed primarily in the liver and metabolizes many environmental molecules and drugs, including several of the opioids. The strong evidence supporting the impact of *CYP2D6* variants on opioid response comes from both its known mechanism of action (bioactivation of the opioids to more potent opioid receptor agonists) and its impact on pain control in clinical trials.[12] Thus, clinical guidelines have been published recommending altered opioid strategies for patients with altered CYP2D6 activities,[12,13,15] and information regarding *CYP2D6* pharmacogenetics has been included in some of the opioid FDA-approved drug labels. However, despite these published guidelines, few providers are using pharmacogenetics when they prescribe opioids. That is due to several barriers that limit its implementation. One of them is the demand for additional data supporting the clinical effectiveness of CYP2D6-guided pain management; the ADOPT-PGx Chronic Pain clinical trial described in this article is designed to address this gap. It is a pragmatic, real-world, multi-site, randomized, controlled, clinical trial. Consistent with the goals of pragmatic, randomized, controlled, clinical trials,[31] this trial should provide real-world evidence of the effectiveness of using CYP2D6 to guide opioid therapies, while maintaining the internal validity of a randomized controlled trial. The pragmatic nature is highlighted by the relatively few inclusion and exclusion criteria, minimal interference with clinical care other than the CYP2D6-guided intervention, and leaving the ultimate decisions up to the clinical providers. This should increase the extrapolation of the results to a wider variety of clinical settings. We expect this trial to provide level 1 evidence[32] that will be key to determining the value of implementing *CYP2D6* testing to guide opioid therapies in patients with chronic pain. The inclusion of large numbers of participants from racial and ethnic minorities and from medically underserved areas and populations should make the results relevant to patients across diverse populations. We do recognize that not blinding the participants and providers is a limitation of the pragmatic nature of the trial. This bias should be limited as we did not actively return the results to the participants prior to the end of the study and, in the real-world clinical implementation of the testing, the providers and patients will know the results. Also, the secondary analysis including the normal metabolizers from both arms may also provide insight into the impact of the intervention arm outside of the impact of the *CYP2D6* genotypes since we do not expect the therapies to be changed in the normal metabolizers. In addition, our outcomes rely on patient-reported outcomes and they can be impacted by perceptions and behaviors, although these should be similar to those that will occur in clinical practice.

Several studies have also focused on testing the association of opioid response with genetic variants in other pharmacokinetic genes and pharmacodynamic genes; however, as highlighted in the literature review of the 2021 CPIC CYP2D6-opioid guideline, strong evidence for the clinical utility of genotyping appears to be limited to *CYP2D6* at this time.[12] We chose to focus our study on codeine, tramadol, and hydrocodone since the CPIC, DPWG, and CPNDS *CYP2D6* guidelines make recommendations for codeine and tramadol and a previous pilot study showing benefit to testing also included hydrocodone[11]; however, some data also suggest that oxycodone prescribing may also benefit from CYP2D6 guidance, particularly for safety reasons, and, therefore, a recommendation to avoid oxycodone in ultra-rapid metabolizers was included. However, based on equivocal evidence, we did not make recommendations to alter therapy in intermediate or poor metabolizer participants treated with oxycodone.[12,33,34] Case reports from patients with chronic pain not only provide additional support for testing but also highlight the potential benefit of panel-based testing and medication reviews for the comprehensive management of drugs used to control pain.[35,36] Thus, several sites do the *CYP2D6* testing for the trial using a pharmacogenetic panel that also includes other pharmacogenes, although the results from the other pharmacogenes were not used prospectively to guide the opioid therapies in this study. The other genes may be candidates for future studies or additional secondary analyses.

Since insurance coverage is also frequently among the top barriers that limit the implementation of pharmacogenetic testing,[37,38] we are collecting claims data to help define the economic implications of CYP2D6-guided management of chronic pain. Because we are recruiting participants from many different healthcare systems, who would have multiple different payers, we will focus on obtaining claims data on participants covered through

Medicare and Medicaid. We expect to obtain these data from approximately half of the enrolled participants. These results should provide the data needed to determine the economic impact of the *CYP2D6* genotyping on healthcare costs; this will be used to explore the value of genotyping and will be additional data to consider for clinical testing reimbursement.

Additional pragmatic prospective clinical trials of the impact of pharmacogenetic testing on patients with chronic pain have been published or are in process. A non-randomized cluster design study in patients with chronic pain showed that those in the *CYP2D6* genotyping arm had improved pain control over usual care.[11] The current study differs in that it is a multi-institution trial and is randomized at the individual participant level, rather than the cluster randomization at the clinic level; however, the interventions are similar. Another ongoing study in patients with chronic pain (Clinicaltrials.gov # NCT04685304) will also assess the impact of *CYP2D6* genotyping compared with usual care; that trial is being conducted at a single institution, but the interventions are similar.

If the results support the implementation of pharmacogenetic testing, the implementation should be able to be adopted rapidly. Implementation guidelines already exist from multiple consortiums. Clinical *CYP2D6* testing is widely available through many institutional and commercial genotyping laboratories.[39] Previous studies have shown that many patients with chronic pain are open to pharmacogenetic testing, and most believe that it has the potential to improve their therapy.[40] Ethics analyses indicate that pharmacogenetic testing would be appropriate if it were able to improve pain control strategies.[41] For example, CYP2D6 also has the potential to serve as a clinical tool to support physician assessments of drug-seeking behavior.[42] When patients present with uncontrolled pain, a CYP2D6 poor metabolizer phenotype may support a patient's complaint. Due to the collective strong evidence currently available, several healthcare systems have already implemented *CYP2D6* testing.[38,43–46]

In summary, we described the design and rationale for the ADOPT-PGx Chronic Pain Clinical trial. We expect that the results from this trial will provide additional data to determine the clinical utility of *CYP2D6* pharmacogenetic testing to guide opioid therapy for patients with chronic pain.

AUTHOR CONTRIBUTIONS

T.C.S., R.A.M., R.B.F., J.T.C., E.C., M.T.E., E.N.E., G.S.G, S.L., K.A.N., A.O.O., H.P., V.M.P., M.R., A.S., S.S., R.S., E.M.T., S.V., K.W., A.G.W., C.R.H., D.V., L.O., H.C., S.V.D., J.F.P., L.A.C., J.A.J., P.R.D. wrote the manuscript. T.C.S., R.A.M., R.B.F., J.T.C., E.C., M.T.E., E.N.E., G.S.G, S.L., K.A.N., A.O.O., H.P., V.M.P., M.R., A.S., S.S., R.S., E.M.T., S.V., K.W., A.G.W., C.R.H., D.V., L.O., H.C., S.V.D., J.F.P., L.A.C., J.A.J., and P.R.D. designed the research. None of the authors performed research or analyzed data as part of this research design manuscript.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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