Implementing Genomics in Practice (IGNITE): *CYP2D6* Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery

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Protocol

1. Project Title:

Implementing Genomics in Practice (IGNITE): *CYP2D6* Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery

2. Investigator(s):

Principal Investigator:

Larisa H. Cavallari, PharmD
Associate Professor
Department of Pharmacotherapy and Translational Research
College of Pharmacy
Director, Center for Pharmacogenomics
Associate Director, UF Health Personalized Medicine Program
University of Florida

Sub-Investigators:

Julie Johnson, PharmD
Distinguished Professor
Department of Pharmacotherapy and Translational Research
Dean, College of Pharmacy
Director, UF Health Personalized Medicine Program
University of Florida

Hari K. Parvataneni, MD
Associate Professor
Department of Orthopedics and Rehabilitation
Division Chief, Adult Arthroplasty and Joint Reconstruction
College of Medicine
University of Florida

Chancellor F. Gray, MD
Assistant Professor
Department of Orthopedics and Rehabilitation
Adult Arthroplasty and Joint Reconstruction
College of Medicine
University of Florida

Petr Starostik, MD
Director of Molecular Pathology
UF Pathology Laboratories
University of Florida

Roger Fillingim, PhD
Distinguished Professor
Dept of Community Dentistry and Behavioral Science
College of Dentistry
Director, UF Pain Research and Intervention Center of Excellence
University of Florida

Yan Gong, PhD
Research Associate Professor
Center for Pharmacogenomics
Department of Pharmacotherapy and Translational Research
College of Pharmacy
University of Florida

Danxin Wang, MD, PhD
Associate Professor
Department of Pharmacotherapy and Translational Research
College of Pharmacy
University of Florida

Study Staff:

Amanda R. Elsey, MHA
Assistant Director, UF Health Personalized Medicine Program
Clinical and Translational Science Institute
University of Florida

Ben Burkley, MS
Scientific Research Manager
IRB Coordinator
Department of Pharmacotherapy and Translation Research
Center for Pharmacogenomics
University of Florida

Erica Elwood, BS
Research Coordinator, UF Health Personalized Medicine Program
Clinical and Translational Science Institute
University of Florida

Evan Waters, BSN, RN
Research Coordinator, Clinical and Translational Science Institute
University of Florida

3. Abstract:

More Americans suffer from pain than are affected by heart disease, cancer and lung disease. Opioids represent the cornerstone of pain management, yet analgesic responses to opioids are widely variable.[1,2] Opioid prescriptions have tripled since 1999, paralleled by increases in opioid-related hospitalizations and deaths, contributing to the opioid epidemic. Approximately 35% of all opioid prescriptions originate from surgeons.[3] Hydrocodone, tramadol, and codeine are among the most commonly prescribed opioids, and the cytochrome P450 enzyme, CYP2D6, is central to generation of highly potent metabolites for these opioids. *CYP2D6* genotype leads to absent, reduced, normal, or increased function, conferring poor (PM), intermediate (IM), normal (NM) and ultrarapid (UM) metabolism phenotypes, respectively. Data suggest avoiding hydrocodone, tramadol, codeine, and oxycodone in PMs, IMs and UMs because of increased risk for poor response (IM and PM) or toxicity (UM). Leveraging our experience from a recent study, we will test the ***hypotheses*** **that *CYP2D6* genotype-guided management of post-surgical pain 1) is feasible, with reduced use of codeine, tramadol, hydrocodone, and oxycodone in PMs/IMs/UMs and 2) will improve post-operative pain control in PMs/IMs**

and reduce DEA Schedule II (C-II) opioids in NMs. Patients scheduled to undergo arthroplasty surgery will be recruited from the UF Health Gainesville and the Villages Orthopedic clinics. Patients will be randomized 2:1 to a genotype-guided versus usual care approach. For patients with CYP2D6 PM, IM or UM phenotype based on genotype or drug interactions, a recommendation to avoid hydrocodone, tramadol, codeine, and oxycodone will be made. In others, tramadol will be recommended, given evidence of its lower potential addiction risk than C-II opioids. Patient Reported Outcomes Measurement Information System (PROMIS) measures will be administered at baseline (within 30 days of surgery) and 2 weeks ± 4 days post-surgery for patients in each arm. Pain scores and assessments of physical functioning, emotional functioning, and mobility from the PROMIS measures and utilization of pain medications during the 2 week period following surgery will be compared between groups.

4. Background:

In the past 10 years, there have been significant advances in defining genetic determinants of drug response. These advances have led to the expectation by many that eventually an individual's personal genetic information will become part of his or her medical record to be used to guide treatment decisions. The UF Health Personalized Medicine Program (PMP) was created at UF to meet this expectation. The initial efforts of the PMP involved implementation of cytochrome P450 (CYP) 2C19 genotyping to guide antiplatelet therapy following percutaneous coronary intervention. We have since implemented *TPMT* testing to guide thiopurine dosing, *CYP2D6/CYP2C19* testing to guide selection of serotonin reuptake inhibitors, *CYP2C19* genotyping to guide proton pump inhibitor doing, and *CYP2D6* testing to guide opioid prescribing in primary care.[4]

The gene for *CYP2D6* is highly polymorphic, with over 100 alleles defined. Functional variation within *CYP2D6* includes SNPs, insertions, deletions, and instances where the gene is deleted or duplicated. Approximately 5-10% of individuals are poor metabolizers (PMs), with no active CYP2D6 enzyme secondary to frameshift mutations (**3, *6*), splicing defects (**4*), or complete gene deletion (**5*). Another 2-11% are intermediate metabolizers (IMs), with significantly impaired enzyme activity secondary to having both a nonfunctional and reduced function *CYP2D6* allele. At the opposite extreme, approximately 1-2% of individuals are ultra-rapid metabolizers (UMs) with *CYP2D6* gene duplication/multiplication. Numerous commonly used drugs inhibit the CYP2D6 protein and can convert one's phenotype to PM or IM, which is called phenoconversion.

Codeine and tramadol are dependent on bioactivation by the CYP2D6 enzyme to morphine and O-desmethyltramadol, respectively, which have 200-fold greater affinity for the μ-opioid receptor than their parent compounds. IMs and PMs have impaired generation of the active metabolites of codeine and tramadol, and may derive little to no pain relief from these drugs.[5] Interestingly, the occurrence of central side effects may not differ between PMs, IMs, and normal metabolizers (NMs) so that while PMs and IMs may get little to no pain relief from opioid analgesics, they may still experience troublesome adverse effects.[6] Conversely, UMs are at increased risk for toxic concentrations of active opioid metabolites, with reports of life-threatening toxicity and death with codeine or tramadol.[7-11] Hydrocodone and oxycodone undergo similar metabolism via CYP2D6 to hydromorphone and oxymorphone, respectively, which have 10- to 40-fold higher receptor affinity than the parent compound. In the case of hydrocodone, tramadol, codeine, and oxycodone, our preliminary data below, and data from others, suggest these drugs should be avoided in PMs and IMs for lack of efficacy and in UM because of toxicity risk.[5]

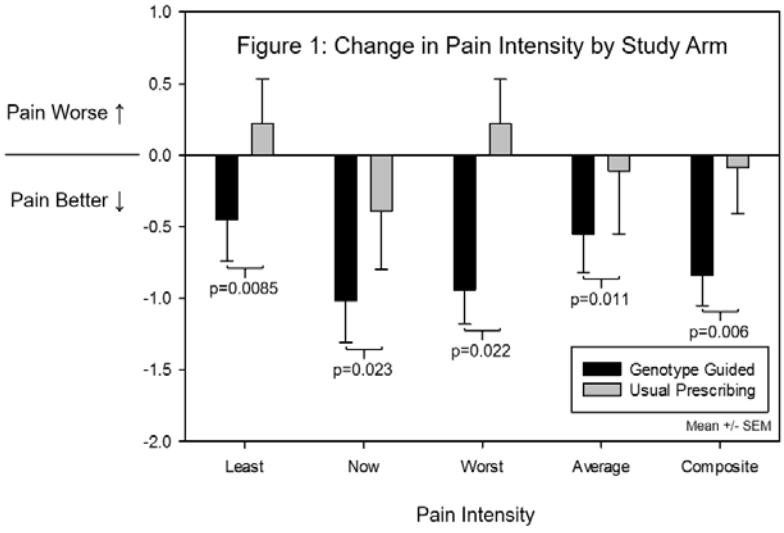
The rapid increase in opioid prescribing in the last 20 years is paralleled by increases in opioid-related hospitalizations and deaths and significant societal costs.[12-14] Opioid misuse contributed to over 60% of all drug-related deaths in the U.S. in 2015, and in the majority of cases, the opioid was obtained legally through prescription.[14,15] **The majority of individuals who misuse opioids report that their motivation for doing so is to relieve physical pain, highlighting the need for better measures to improve pain control and opioid prescribing**.[16] A major gateway to chronic opioid use arises from post-operative opioid prescribing, with evidence of persistent opioid use in approximately 6% of opioid naïve individuals receiving a new opioid prescription after an outpatient surgical procedure.[17] With this risk, there is a critical need to identify ways to control pain while minimizing use of highly addictive opioids, like hydrocodone and oxycodone.

Guidelines support *CYP2D6* genotype-guided use of opioid analgesics,[5] but this is rarely done in clinical practice. We propose a pilot trial in patients with acute post-surgical pain in which we will make recommendations based on *CYP2D6* genotype and CYP2D6 enzyme inhibitor drug interactions that can convert individuals to the PM or IM phenotype. In PMs, IMs and UMs, we will recommend avoidance of hydrocodone, tramadol, codeine, and oxycodone and for NM, tramadol will be recommended as the preferred opioid, given its opioid and non-opioid mechanisms and purported lower risk for misuse.[18,19] One study suggested the potential for abuse and dependence with tramadol in patients with chronic non-cancer pain was significantly less than for hydrocodone, and not different from that of non-opioid pain relievers.[18] The preference toward tramadol is consistent with the Enhanced Recovery After Surgery Pathway, which proposes a strategy to limit peri- and post-operative opioid use and combat the opioid epidemic through primary use of non-opioid agents and techniques and tramadol as the preferred opioid for breakthrough pain because of its evidence for lower addition.[18-20] We will examine the effect of having *CYP2D6* genotype information on pain management and pain control. Findings will inform a larger trial of the efficacy of a genotype-guided approach to pain management. The ultimate goal of this line of research is to reduce the significant societal burden associated with pain. While not directly assessing the opioid epidemic, reduced use of more potent and addictive opioids for the management of post-surgical pain may lead to less persistent opioid use.

4a. Preliminary Studies:

***CYP2D6* genotype-guided pain therapy.** We conducted a pragmatic clinical trial to test the potential clinical benefit of *CYP2D6* genotype to guide tramadol, codeine, oxycodone and hydrocodone in patients with chronic pain (NCT02335307). We enrolled 480 patients with ≥3 months pain from 9 different primary care clinics at UF Health or the OneFlorida Network. Patients were randomized 2:1 to a genotype-guided intervention or control group (usual care, with genotype reported at study end). NIH-developed and validated Patient Reported Outcomes (PRO) Measures Information System (PROMIS) pain measures were collected from all patients at baseline and 3 months. For the genotype group, genotype data were available approximately 7 days after the baseline clinic visit. Patients were defined as phenotypically CYP2D6 UMs, NMs, IMs or PMs based on their *CYP2D6* genotype and use of strong or moderate CYP2D6 inhibitors (according the FDA guidelines).[21] A clinical pharmacist-written consult note was provided on all patients with an actionable (PM, IM, or UM) phenotype. Strong recommendations were made in IMs and PMs against tramadol and codeine, where the impact of CYP2D6 is clear. Recommendations against oxycodone and hydrocodone were more moderate. Acceptance of the recommended changes was at the physician's discretion. At baseline, median pain intensity based on PROMIS measures was 6.7/10, and 438/480 (91%) were taking an opioid, which included 164 on tramadol, 96 on hydrocodone, 11 on codeine, 125

on oxycodone and 42 on other opioids. Based on genotype, 1% were UM, 11% were IMs or PMs, and when considering phenoconversion by strong or moderate CYP2D6 inhibitors, 29% were IMs or PMs. Patients treated with tramadol, hydrocodone or codeine at baseline had improvements in the genotype-guided arm in pain intensity. In the group for whom the benefit was expected (IMs and PMs), analyses revealed significantly greater improvements for genotype-guided versus usual care for numerous pain intensity subscales (**Figure 1**). A clinically meaningful 30% reduction in pain score was observed in 24% of genotype guided versus 0% of usual care patients (p=0.04). There was also a significant reduction in pain intensity when also considering hydrocodone use at baseline (p=0.02).



5. Specific Aims:

The specific aims of our pilot study are to: 1) test the feasibility of a genotype-guided opioid prescribing approach for patients undergoing an outpatient surgical procedure, a group at high risk for persistent opioid use; and 2) evaluate the effect of genotype-guided post-surgical pain management on pain control and opioid prescribing. This will be a randomized, open-labeled pilot pragmatic clinical trial. A total of 320 patients will be recruited from the UF Health Gainesville and the Villages Orthopedic Clinics during their Initial Evaluation for total joint (hip or knee) replacement once the decision for surgery is made. For patients randomized to the genotype-guided arm, a saliva or buccal cell sample will be collected unless venipuncture is done for other reasons and then a blood sample will be collected for genotyping. Genotyping will be performed in the UF Health Pathology Laboratory and results placed in the electronic health record (EHR). For patients in the usual care arm, a genetic sample will be collected for clinical genotyping at the end of the study. At baseline (within 30 days of surgery) and 2 weeks ± 4 days after surgery, all patients will be asked to complete the PROMIS measures for assessment of pain intensity, physical functioning, emotional functioning, mobility, and a measure of medication misuse. We will also assess utilization of pain medications during the 2 weeks ± 4 days following surgery. We hypothesize that *CYP2D6*-guided post-operative pain management is feasible, with reduced use of codeine, tramadol, hydrocodone, and oxycodone in patients with the PM, IM, or UM phenotype, and will improve pain control in PMs and IMs and reduce use of more addictive opioids (i.e. DEA schedule II opioids) in patients with the NM phenotype.

6. Research Plan:

The study will be a randomized, open label pragmatic clinical trial in 320 patients undergoing total joint arthroplasty, who will be randomized to genotype-guided opioid therapy or usual care.

We will collect data on the implementation success metrics, PROs via PROMIS measures, and for opioid utilization measures, we will collect proportion of patients prescribed specific opioids and self-reported opioid use, since patients may not take any or all of the opioid prescribed.

Inclusion Criteria. A total of 320 patients scheduled to undergo total joint arthroplasty at UF Health will be recruited from the UF Health Gainesville and the Villages orthopedic surgery clinics. Participants must be 18 years or older and have a planned or scheduled primary unilateral total hip or knee arthroplasty procedure. The planned or scheduled procedure must be completed within 6 months of the last participant enrolled.

Exclusion Criteria. Patients scheduled to undergo a revision or bilateral procedure; receiving chronic opioid therapy, defined as use of opioids on most days for >3 months; or with an allergy to opioids will be excluded.

Participant Recruitment Methods. Patients typically have 2 visits to the UF Orthopedic Surgery clinic prior to surgery: an Initial Evaluation visit when the decision about surgery is made and 2) a Pre-Operative visit within 1 month of the procedure when a plan for post-operative pain management is made. During either the Initial Evaluation (decision for surgery visit) or Pre-Operative visit, patients meeting eligibility criteria will be approached by the research coordinator about study participation. The patients could also be approached via telephone, after their initial clinic evaluation to discuss consenting over the phone with the study coordinator after the physician had discussed the study during the initial evaluation appointment. The patient will be read the screening script by the coordinator to ensure the patient is eligible for the study and interested in participating. If the patient would like to enroll in the study after the screening telephone call, 2 copies of the informed consent form and a buccal cell collection kit will be mailed to the patient. Once the patient has received the research kit, the study coordinator with call the patient and read the follow up script as needed. The patient will mail the signed informed consent form and completed buccal swab sample to the study coordinator using the preaddressed paid envelope the patient will be provided. After providing written informed consent, patients will be randomly assigned to genotype-guided opioid therapy or usual pain management. A DNA sample will be collected from all patients, regardless of randomization, by saliva (via mouthwash swish and expectorate collection) or buccal cell (via buccal brush), unless venipuncture is done for other reasons and then a blood sample will be collected for genotyping. If the genotype fails with the initial sample collection, the patients will be mailed a kit for collection of a saliva or buccal cell sample for retesting.

For patients in the genotype arm, *CYP2D6* genotyping will be done in the CAP/CLIA-licensed UF Health Pathology Laboratory at Rocky Point with results reported in the EHR. It is expected that results will be reported prior to surgery in the absence of any genotyping error. Patients will be categorized as CYP2D6 PM, IM, NM, or UM based on *CYP2D6* genotype/activity score and FDA guidance on drug interactions.[22] Strong inhibitors (e.g. bupropion, fluoxetine, paroxetine) phenoconvert patients to PMs, with moderate inhibitors (e.g. duloxetine, fluvoxamine) reducing CYP2D6 activity scores by 50%.[5,23,24] Using a standardized consult note, as we are using for an on-going study in cancer pain patients (NCT02664350), recommendations will be made to avoid tramadol, hydrocodone, codeine, and oxycodone in PMs, IMs, and UMs and to use an alternative opioid (e.g. morphine, hydromorphone) or non-opioid (e.g. NSAID). Consideration of tramadol as the first line opioid will be recommended for NMs. Patients randomized to usual care will have their DNA sample collected at the Initial Evaluation visit and stored until they have completed the 2 week follow-up, at which time, the sample will be genotyped with the result reported in the EHR. This approach was successfully used in our previous study in chronic pain. Genotyping will be funded by the grant. Patients will be compensated in the amount of $25 gift certificate for their participation. Study participation will be terminated for any patient

randomized into the usual care arm who gets genotyping done for clinical care before study completion. These patients will receive $10 compensation for study participation.

Patients in both arms will be asked to complete surveys for PROs at the Pre-Operative visit (within 1 month of surgery) or via phone call within 30 days prior to surgery. Patients will be asked the PROMIS Pain intensity survey and about opioid consumption at 48 hours ± 24 hours and again at 1 week ± 4 days post-surgery. At 2 weeks ± 4 days post-surgery, utilizing the PROMIS measures developed with the NIH Common Fund (www.nihpromis.org). Surveys will be completed with the study coordinator in clinic or by telephone after their clinic visit, or if patients prefer, electronically through a link sent to them to be completed prior to their surgical procedure. Outcome measures for the proposed study were selected based on guidance in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT),[25,26] which recommends that pain outcome studies assess the domains of pain, physical functioning, and emotional functioning. The specific PROs we will assess are shown in **Table 1**. These measures are well adapted for use in the clinical setting, and employ a Computer Adaptive Test (CAT) approach that minimizes respondent burden by reducing the number of questions needed to arrive at a valid PRO. We have significant experience administering the PROMIS measures to assess pain intensity using an IPAD tool from our recently completed study in patients with chronic pain. We will also assess how well patients are able to do their usual activities with the HOOS or KOOS survey.

Table 1. PROMIS Measures to be employed

Scales	Subscales
Pain Intensity	Worst and average pain intensity in last 7 days and current pain
PROMIS 43 (7 subscales + 1 pain intensity question)	Physical functioning: • Pain interference • Physical function • Sleep disturbance • Social role & activities functioning Emotional functioning: • Fatigue • Anxiety • Depression
Others	• Prescription pain medication misuse

Data will be recorded directly into the REDCap server. Patients desiring survey completion on a personal electronic device will receive a link by Short Message Service (SMS) to their cell phone using TWILIO through REDCap or email. For collection of data in those not completing surveys on personal electronic devices, or not completing them within specified time windows, we will use a call center approach to data collection. The UF Center for Quality Medication Management (CCQM) provides medication therapy management in a call-center model, with vast experience scripting for consistent data collection, and speaking to patients about drug therapy and therapy-related outcomes. Pharmacy technicians in the CCQM will be given a telephone script to use for calling study participants for survey completion.

Data collection. In addition to data from the PROMIS measures, we will collect the following patient information from the EHR: name, medical record number, demographics (age, sex, race, ethnicity), past medical history, social history (smoking status), surgical procedure scheduled, medications (chronic, pre-operative, post-operative, and discharge medications), use of regional anesthesia or nerve block, hospital length of stay, use of opioids at 3 and 6 months (to assess persistent opioid use). In addition, opioid consumption will be assessed at the 2 week (± 4 day) data collection point via patient interview.

Outcomes. The primary outcomes are feasibility of the clinical implementation (Table 2) and opioid utilization. The secondary outcomes will be pain intensity, physical functioning, emotional functioning, and mobility at 2 weeks ± 4 days post operatively.

Data analysis. *For the primary analysis*, we will collect data on the implementation success metrics in **Table 2**. For opioid utilization measures (morphine equivalent dose (MED), schedule IV/II opioid use), we will determine the proportion of patients prescribed specific opioids and self-reported opioid use, since patients may not take any or all of the opioid prescribed. Opioid use (proportion) will be compared between arms by χ^2 analysis or Fisher's exact test. *For our secondary outcome of pain intensity*, we will create a composite score of current pain and worst and average pain in last 7 days from the pain intensity subscales. We will use pain intensity at 14 days post-surgery (with a ± 4 days data capture window). Comparisons between the genotype-guided and usual care groups will be by analysis of covariance (ANOVA), adjusting for baseline pain scores and other baseline differences between the two groups and accounting for MED and/or use of opioids other than tramadol, codeine, hydrocodone, or oxycodone. While beyond the scope of this pilot, we also plan to collect data on prevalence of new persistent opioid use at 6 months (in those who were opioid naive in the year prior to the study)[171] and differences between groups in the PRO of prescription pain medication misuse.

Table 2. Clinical Implementation Success metrics

- % of patients agreeing to participate
- % of patients in genotype arm with a genotype leading to a clinical recommendation for alternative therapy
- % of patients in whom a genetic-guided recommendation is accepted by the clinician
- If recommendation is not accepted, what are the prevailing reasons
- Patient reported opioid use by CYP2D6 phenotype

Power analysis. We acknowledge that the proposed trial will have insufficient power to examine PROs (e.g. pain intensity). However, these data will be collected to provide preliminary data on the effects of genotype-guided therapy on PROs to inform a future larger pragmatic clinical trial, and also to document that there are not obvious trends of the genotype-guided approach leading to worse pain control, which in turn could lead to worse post-surgical outcomes. Moreover, if we assume that 25% of patients in the implementation arm will be a PM, IM, or UM (based on genotype and drug interactions) and that codeine, tramadol, hydrocodone, and oxycodone will be avoided in these patients, whereas the remaining 75% of patients in the implementation arm will be prescribed tramadol and nearly all (i.e. 95%) of controls will be prescribed tramadol, codeine, hydrocodone, or oxycodone we will have >80% power, with an alpha of 0.05, to detect a difference in use of codeine, tramadol, hydrocodone, or oxycodone between arms.

Resource Sharing Plans

All materials developed for this study (including REDCap templates) will be made available to the larger UF and scientific community. Genotype data will be available in EPIC, and thus can be accessed (deidentified) through the Integrated Data Repository (IDR) for future studies. As an NIH funded study, we will use a consent process that allows sharing of de-identified data with other investigators or through dbGaP. We will include a section in the consent form that allows patients to choose whether or not to share de-identified genotype data with the NIH using the dbGaP database. We will share pharmacogenetic data and core phenotypes of interest with the larger scientific community through dbGaP if the patients give permission for this type of data sharing.

Data Safety Monitoring Plan

Based on assessments of the risk-to benefit ratio, the risk level associated with the study is low. All risks have been described in the consent form.

Plan for Safety Review:

Monitoring procedure for safety, efficacy, eligibility, and data management are delineated in the protocol. The PI will adhere to the protocol as described. Only subjects who meet the protocol inclusion criteria will be enrolled.

Plan for adverse event reporting:

Monitoring for documentation of an adverse event, whether anticipated or unanticipated, is the responsibility of the principal investigator who will maintain oversight but may delegate collection of information related to this function to other study team member. In term of SAFETY monitoring, all adverse events spontaneously reported, elicited, or observed by the investigators will be recorded.

All Serious Adverse Events, should they occur, whether study-related or expected, will be documented on a Case Report Form, under Adverse Event section in the Patient's binder, reported by the principal investigator to the IRB within five (5) working days.

In addition, the principal investigator will follow the reporting requirements for serious and unexpected adverse events outlined in the UF IRB Adverse Event Evaluation and Reporting Guide. All unanticipated, serious, fatal and/or life-threatening adverse events will be reported to the UF IRB. Aggregate reports of adverse events will be prepared on an annual basis or at the end of the study, whichever may occur earlier and forwarded to the IRB at annual review.

Plan for data management:

Case Report Form (CRF) within REDCap will be used for each subject. To protect the participant's right of privacy, subjects' individual records related to the study and will be stored in locked cabinets with limited access, and electronic files will be kept in secured database. A de-identified dataset from the database using a patient identification number will then be shared with statistician for analysis. During the study, data will be analyzed as it becomes available by Dr. Larisa Cavallari. No early closure is planned because of the limited scope and projected low risk of the study.

There is a prospect of direct benefit to individual subjects, in that genotype information could lead to improved pain management post operatively.

Nevertheless, in the absence of a direct benefit, the study may advance the field by providing an increased understanding of the utility of CYP2C6 genotyping for post-operative pain control. Such understanding is deemed essential for broader dissemination of genotyping into clinical care.

9. Conflict of Interest:

Publications that may result from such research can enhance the reputation of the investigators.

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UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form which describes the study in some detail. A member of the research team will describe this study to you and answer all of your questions. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits to which you would otherwise be entitled if you choose not to participate in this study or to withdraw. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study?

Implementing Genomics in Practice (IGNITE): CYP2D6 Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery

3. Who do you call if you have questions about this research study?

Principal Investigator: Larisa H. Cavallari, PharmD, Phone: 352-273-8245

4. Who is paying for this research study?

The sponsor of this study is the University of Florida Clinical and Translational Science Institute's Learning Health System Initiative.

5. Why is this research study being done?

The purpose of this research study is to find out if information about a patient's genetic makeup (DNA) will help doctors better manage pain after hip or knee replacement surgery. Genetic makeup is what determines a person's body traits, such as height and eye color. Genetic makeup differs from person to person, which is why one person's body traits are different from another person's. By doing this study, the investigators can find out if your genes can help doctors choose better medicine for controlling your pain after surgery. This will be done through questionnaires to be completed by you at the beginning and end of your participation. You are being asked to be in this research study because you are scheduled for hip or knee replacement surgery.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

You will receive the same clinical care to manage your pain after your surgery that your doctor would usually provide.

7. What will be done only because you are in this research study?

If you choose to participate in this study you will be asked to provide a 2 ml (one-half teaspoon) saliva sample by spitting into a special tube or cheek tissue by using a soft brush or swab. This saliva or cheek sample will be used to collect your DNA. If you are getting blood work done as part of your clinical care on the day you are consented, then a 5 ml tube of blood may be collected for the research study instead of the saliva or cheek sample. Your genetic make-up will be determined from the DNA in your saliva, cheek, or blood.

You will be randomly assigned (like the flip of a coin) into either the test group or the control group. Research studies of this type usually compare a "test" group and a "control" group when trying to determine if information gained from genetic makeup is helpful to doctors in making decisions about what medication to prescribe to patients.

If you are a patient in the "test" group, your genetic test results will be shared with your doctor and placed in your medical record to help with selecting your pain medication after surgery. Your results may influence what pain medication your doctor prescribes for you. If your first DNA sample does not produce results, we will mail you a genotyping kit for re-collection of a saliva or buccal cell sample to test again. This is so that your genetic results can be available to your provider before your surgery.

If you are assigned to the control group, your doctor will manage your pain per usual care until your participation ends. You will be genotyped at the end of your participation, with your results placed in your medical record and shared with your doctor. Your genetic test results will be made available to your doctor at the end of your participation in this study, after you complete the 2 week follow up survey. Your results may influence what pain medication your doctor prescribes for you in the future.

You will be asked to complete a short questionnaire within one month before your surgery and again as close as possible to 1 week and 2 weeks after your surgery. These questionnaires are for research purposes. The questionnaires can be completed with the study coordinator in the clinic, by telephone, or electronically though a link sent to you by Short Message Service (SMS) to your cell phone or email. If you choose to complete the questionnaires over the phone, you will receive a call from UF College of Pharmacy call center. The questionnaire will ask about how bad your pain is and how it affects your daily activities and about prescription medication misuse in the past. You will also be asked as close to 2 weeks after your surgery about how much of your pain medication you took. Your doctor and other researchers will use this information to compare how well your pain is controlled before and after the study. We will compare how well pain was controlled in patients who had their genetic information used for pain management after surgery and those who did not have this information used.

Researchers for the study will look at your medical record for use of opioids at 3 and 6 months after surgery to see if you are still taking these medications.

If you have any questions now or at any time during the study, please contact one of the research team members listed in question 3 of this form.

8. How long will you be in this research study?

Your active participation in the research study will last until the completion of the questionnaire approximately 2 weeks after your surgery. Researchers for this study will also look at your medical record to identify whether you have been prescribed opioids at 3 and 6 months after surgery. Your genetic information will be stored in your medical record indefinitely.

9. How many people are expected to take part in this research study?

It is anticipated that up to 320 subjects will participate in this research study

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

10. What are the possible discomforts and risks from taking part in this research study?

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Additional information can be obtained at: http://irb.ufl.edu/gina.html or call 1-800-669-3362. If you think this law has been violated, it will be up to you to pursue any compensation from the offending insurance company and/or employer. Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. Questions 17-21 in this form discuss what information about you will be collected, used, protected, and shared.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You have been informed that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. That is, if you give written consent for the release of information, we cannot withhold that information and we cannot hold responsibility for how that person may use your information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. If we learn about child abuse, elder abuse, or intent to harm yourself or others, we will report that information to appropriate authorities.

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. If you are already enrolled in another research study, please inform one of the research team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the research team members listed in question 3 in this form.

11a. What are the potential benefits to you for taking part in this research study?

By providing your doctor with your genetic information and questionnaire responses, you may experience better pain control after surgery.

11b. How could others possibly benefit from this study?

Other patients could one day experience better pain management after surgery due in part to the results of this study.

11c. How could the researchers benefit from this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator listed in question 3 of this form may benefit if the results of this study are presented at scientific meetings or in scientific journals.

12. What other choices do you have if you do not want to be in this study?

You can have the genetic test determined as part of your clinical care without participating in this study. This can be done before your surgery and should be discussed with your doctor. You would be responsible for the cost of the test.

If you choose not to participate in this study, your doctor will continue to provide you with the best possible pain management without the use of your genetic information. In the future, if you decide you do want your doctor to use your genetic information for pain management, please discuss this with your doctor.

13a. Can you withdraw from this study?

You are free to withdraw your consent and to stop participating in this study at any time. If you do withdraw your consent, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you decide to withdraw your consent to participate in this study for any reason, please contact one of the research team members listed in question 3 of this form. They will tell you how to stop your participation safely.

If you have any questions regarding your rights as a research subject, please call the Institutional Review Board (IRB) office at (352) 273-9600.

13b. If you withdraw, can information about you still be used and/or collected?

If you discontinue participation in the study (withdraw), the information about you collected up until the time you withdraw can still be used and stored in the data repository in accordance with your choice.

13c. Can the Principal Investigator withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

- At the discretion of the principal investigator or study physician based on what is best for your health and safety.
- If you are a control patient and you or your physician request your genetic test results prior to study completion.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

Study Services

The Sponsor will pay for all services required as part of your participation in this study as described above in the question *"What Will Be Done Only Because You Are In This Research Study*". If you receive a bill for these services, please contact Dr. Larisa Cavallari at (352) 273-8245.

Items/Services Not Paid for by the Sponsor

All other medical services provided to you that are not directly required by this study will be billed to you or your insurance company in the usual manner.

15. Will you be paid for taking part in this study?

You will receive a total of $25 for participating in this study. A $25 VISA gift card will be provided after your complete your final questionnaire.

If you are in the control group and you or your physician chooses to withdraw your participation to have the genetic information used for clinical care before your study participation is complete, you will receive a $10 VISA gift card for your study participation up to the point of your withdrawal.

Your payment for participation in this research study is handled through the University of Florida's Human Subject Payment (HSP) Program. Your information which will

include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (HSP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity.

If you have any problems regarding your payment contact the study coordinator.

16. What if you are injured because of the study?

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. Please contact your insurance company for additional information.

The Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is routinely offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact one of the research team members listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this study.

17. How will your health information be collected, used and shared?

If you agree to participate in this study, the Principal Investigator will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the Principal Investigator needs your authorization The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving

study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- Complete past medical history
- Records of physical exams
- Laboratory and genetic test results
- Results of completed questionnaires
- Medication records
- Clinical outcomes

This information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will only include information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, photographs, or other codes that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the limited data set are required in order to protect your identity and confidentiality and privacy.

If you agree to share your genetic information with the National Institutes of Health's database of genotypes and phenotypes (dbGaP) by signing the second addendum below, the study coordinator will communicate to the laboratory that your de-identified data may be submitted to dbGaP. Your PHI will not be provided to dbGaP, only the result of your genetic test and your non-identifiable demographic information. If you have any questions about what will be shared with dbGaP please ask one of the research study staff listed in question 1 of the "Consent Addendum" attached.

18. For what study-related purposes will your protected health information be collected, used, and shared with others?

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, through your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- To determine the effectiveness of your pain medication relative to your genetic information
- To determine how your survey responses about your pain management are related to your genetic information

Once this information is collected, it becomes part of the research record for this study.

19. Who will be allowed to collect, use, and share your protected health information?

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

- The study Principal Investigator (listed in question 3 of this form) and research staff associated with this project.
- Other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures.
- The University of Florida Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research).

20. Once collected or used, who may your protected health information be shared with?

Your PHI may be shared with:

- The study sponsor (listed in Question 4 of this form).
- United States and agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections.
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments.

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

21. If you agree to take part in this research study, how long will your protected health information be used and shared with others?

Your PHI will be used and shared with others until the end of the study, unless you decide to have your information stored in dbGaP. Information stored in dbGaP will be used/shared with others indefinitely.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the Principal Investigator.

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization	Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described in sections 17-21 above. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing	Date

Consent to Collect and Store Your Genetic Data for Future Research

As part of the research project the study staff are seeking your consent to store your genetic data.

Reason for Storing Your Data:

You have recently agreed to participate in the research study listed above, which is funded by the National Institutes of Health (NIH). That research study involves determining certain genetic information about you. The NIH has a policy of sharing genetic information with other researchers to help further new discoveries on disease treatment and cures. Genetic factors are those that people are born with and that can affect other family members. Your genetic information that will be stored in this federal data bank (dbGaP), will be determined by the research study you have already agreed to.

The person in charge of the research project you agreed to (also known as the Principal Investigator) or a representative of the Principal Investigator will describe this data sharing to you and answer all of your questions. Your participation in allowing your data to be shared and stored in this NIH data bank is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. If you choose not to participate in this data banking and data sharing study you will not be penalized or lose any benefits that you would otherwise be entitled to.

What will Happen to Your Genetic Data:

If you agree to this data banking and data sharing study, your genetic data and any other data that is collected in the study will be placed into a secure location(a large computer) at the University of Florida (UF). Once the other study you agreed to (listed above) is completed, your genetic data and other data collected on you during that study will have all identifiable information removed and then be sent to the NIH data bank. Your de-identified data that is sent will be given a unique ID number, but only those at UF or your affiliated institution will be able to match this unique ID number to identify you.

Who Can Use Your Stored Data:

At the NIH, de-identified genetic data that has been collected from you and other participants may be given to researcher from around the country who apply to the NIH to receive de-identified data to use in their research projects. This request will first have to be approved by an NIH committee that oversees the release of the data. Once the NIH committee approves the release of the de-identified data, the researcher will have to get local Institutional Review Board (IRB - an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research) approval before they can start their study and use this de-identified genetic data.

At the NIH, since your data is de-identified in the data bank, neither you nor UF nor your affiliated institution will receive any information when data is used in future research or receive any results from that future research.

Benefits to You in Storing Your Data:

There is no direct benefit to you for participating in this data bank.

Risks to You in Storing Your Data:

At NIH:

- Risk of Identification: The genetic data being sent to the NIH Data Bank is de-identified, however there is a slight chance that identifiable information may be mistakenly sent.
- Risk Associated with the Freedom of Information Act: Your information that is sent to the NIH will be kept in an NIH data bank and will, thereby, become U.S. government records that are subject to the Federal Freedom of Information Act (FOIA). As an agency of the Federal government, the NIH is required to release government records in response to requests under the federal Freedom of Information Act (FOIA), unless the records are exempt from release under one of the FOIA exemptions. The NIH believes that the only release of your data under such a request would be your data with the unique ID number removed.
- Risks Associated with Law Enforcement Access: It is possible that law enforcement agencies could request access to the de-identified genetic data within the NIH data bank and, for example, search for matches to DNA data collected as part of some criminal activity. While this is expected to be rare, such requests may be granted by the NIH. Law enforcement officials might then try to identify you by requiring your study doctor to release the key to the unique ID number which could identify you. However, the release of identifiable information by your study doctor may be protected by the Certificate of Confidentiality.

  In order to better protect access to your genetic information, both UF and the NIH have obtained a Certificate of Confidentiality. Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect researchers from being forced to release research records, which in this case is your genetic information. These Certificates allow the researchers and others who have access to research information to refuse to release information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Risks to Specific Populations, Groups, and Communities: Medical research has already shown that some populations demonstrate a higher likelihood to develop certain medical diseases than others. It is possible that if you have some rare condition or rare physical characteristics, that someone could identify you based on the de-identified data in the NIH data bank.

Can You Withdraw Your Consent to Store Your Data?

If you decide that your genetic data can be kept for research but you later change your mind, tell the study staff listed in question #1 of the "Consent Addendum" who will inform the Federal Data bank to remove your de-identified data from the data bank. There will be no cost to you for this storage of your de-identified genetic data.

Do You Agree to Participate?

Please review the statement below and initial by your choice:

I agree to have my de-identified genetic data shared with the NIH databank (dbGaP) to be used for future unknown research.

Initials _____ YES Initials _____ NO