CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):	16-gene pharmacogenetic panel test
STUDY NUMBER(S): IRB Number	851447
PROTOCOL(S) TITLE:	**P**ha**R**macog**E**netic-guided **C**ho**I**ce of post-**S**urg**E**ry analgesics (**PRECISE**)
REGULATORY SPONSOR:	University of Pennsylvania Institutional Review Board
FUNDING SPONSOR(S):	University of Pennsylvania Penn Center for Precision Medicine
ORIGINAL PROTOCOL DATE:	May 24, 2022
VERSION NUMBER:	v 5.0
VERSION DATE:	August 29, 2023

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Penn Center for Precision Medicine Perelman School of Medicine University of Pennsylvania
STUDY TITLE:	**P**ha**R**macog**E**netic-guided **C**ho**I**ce of post-**S**urg**E**ry analgesics (**PRECISE**)
STUDY ID	[IRB # 851447]
PROTOCOL VERSION	v 5.0

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name:	Sony Tuteja, PharmD, MS	Signature
Affiliation:	4249 – DM-Translational Medicine and Human Genetics	Date
Co-Investigator Name:	Glenda Hoffecker, PharmD	Signature
Affiliation:	4249 – DM-Translational Medicine and Human Genetics	Date
Co-Investigator Name:	Mary Deagostino-Kelly, MD, MSCE	Signature
Affiliation:	Department: Obstetrics and Gynecology	Date
Co-Investigator Name:	Stefan Gysler, MD, MHS	Signature
Affiliation:	Department: Obstetrics and Gynecology	Date
Co-Investigator Name:	Lakeisha Mulugeta-Gordon, MD	Signature
Affiliation:	Department: Obstetrics and Gynecology	Date

Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reactions
AS	Activity score
CAP	College of American Pathologists
CDS	Clinical Decision Support
CLIA	Clinical Laboratory Improvement Amendments
CNV	Copy number variation
CPIC	Clinical Pharmacogenetics Implementation Consortium
CYP	Cytochrome P450
DGI	Drug-gene interactions
DNA	Deoxyribonucleic acid
EMR	Electronic medical record
IM	Intermediate metabolizer
LOS	Length of stay
MME	Morphine milligram equivalence
NSAID	Non-steroidal anti-inflammatory drug
PDMP	Prescription drug monitoring program
PGx	Pharmacogenetic
PM	Poor metabolizer
POD	Postoperative day
Postop	Postoperative
UM	Ultrarapid metabolizer

1 STUDY SUMMARY

1.1 Synopsis

Title:	**P**ha**R**macog**E**netic-guided **C**ho**I**ce of post-**S**urg**E**ry analgesics (**PRECISE**)
Short Title:	PRECISE
Study Description:	Opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are used to prevent or treat acute postoperative (postop) pain yet are associated with adverse drug reactions (ADRs), resulting in an increase in medical costs and hospitalization length of stay (LOS). Efficacy and toxicity of opioid pain medications (tramadol, codeine, and hydrocodone) and NSAIDs, (celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam) are impacted by pharmacogenetic (PGx) variants (i.e., CYP2D6 or CYP2C9, respectively). We hypothesize that availability of a multi-gene PGx panel test with a pharmacist consult will increase PGx test utilization, provide tailored pain medication recommendations and improve patient outcomes. This is a randomized pilot implementation study to determine the feasibility of integrating a preemptive PGx panel test into clinical care to guide analgesic selection and dosing in postop gynecologic surgery patients. Effectiveness of the PGx-guided approach will be determined by comparing the numeric pain scores, overall opioid consumption as assessed by morphine milligram equivalence (MME) per day, and incidence of opioid/NSAID-related ADRs to a control group receiving usual care.
Objectives:	Implementation Aims: 1. To determine the feasibility of integrating a PGx panel test in the EMR with a pharmacist PGx consult. 2. Determine the fidelity to genotype-guided pharmacotherapy recommendations. Effectiveness Aims: 3. To determine if PGx testing will improve the patient self-reported numeric pain scores 4. To determine if PGx testing will reduce MME 5. To determine if PGx testing will decrease ADRs resulting from their pain regimen.
Primary Endpoint:	1. The proportion of PGx test results returned prior to surgery.

	2. The proportion of dose modifications and medication selections made in agreement with the genotype-guided dosing recommendations for analgesic medications. [Time Frame: up to 14 days after surgery]
Secondary Endpoints:	1. Mean patient self-reported numeric pain scores on POD 0, 1, & 2 (only while admitted) and POD 3, 7, & 14 in each group. [Time Frame: 14 days after surgery] 2. The total MME consumption between intervention and control groups on POD 0-7 and POD 1-14). [Time Frame: 14 days after surgery] 3. The frequency of pain medication related ADRs. 4. Baseline provider attitudes toward and knowledge of PGx testing as assessed by a questionnaire. [Time Frame: Prior to start of study and provider education] 5. Post-study patient experience with PGx testing as assessed by a questionnaire. [Time Frame: 30 days after surgery]
Study Population:	Inclusion criteria 1. Able and willing to provide informed consent 2. Assigned female at birth and aged 18 years or older at the time of study initiation 3. Major gynecologic surgery indicated and planned for hysterectomy, myomectomy, exploratory laparotomy, and open abdominal surgery 4. Willing to provide a buccal swab for PGx testing and comply with all study-related procedures Exclusion criteria 1. Receiving chronic opioid therapy defined as ≥ 3 consecutive months of 1-month prescriptions for an opioid (determined by review of the prescription drug monitoring program [PDMP]). 2. Pregnancy 3. Breastfeeding 4. Treating physician does not want subject to participate
Phase:	N/a
Description of Sites/Facilities	1. Jordan Center for Gynecologic Cancers Perelman Center for Advanced Medicine (PCAM) Abramson Cancer Center, West Pavilion, 3rd Floor 3400 Civic Center Boulevard Philadelphia, PA 19104 2. Helen O. Dickens Center for Women's Health: Hospital of the University of Pennsylvania 1 West Gates

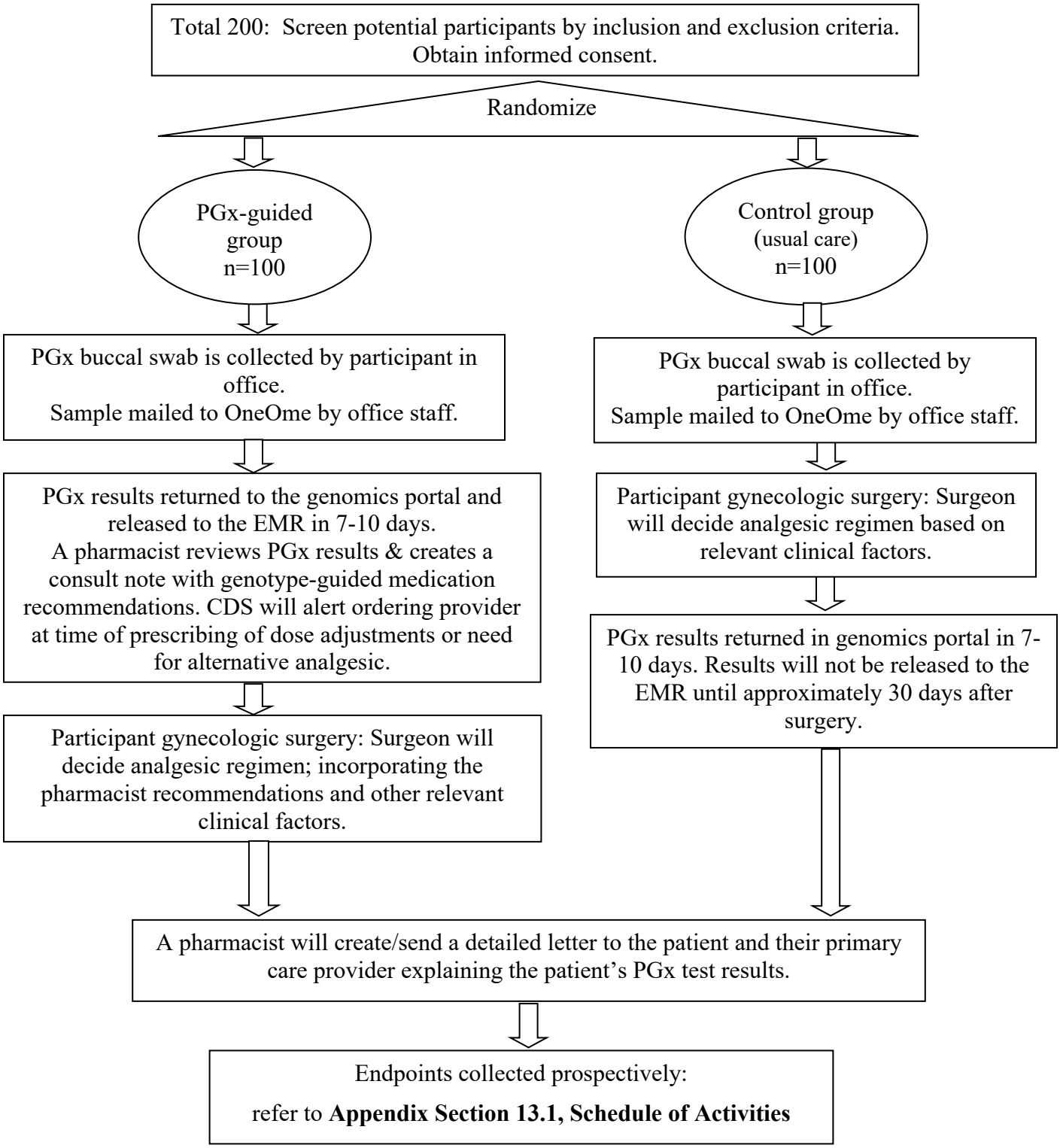
	3400 Spruce Street 3. Penn Health for Women Radnor Floor 3, Suite 302 North 145 King of Prussia Road Radnor, PA 19087 4. Penn Ob/Gyn Associates Suite 371 3701 Market Street Philadelphia, PA 19104 5. Penn Health for Women University City 12th floor 3737 Market Street Philadelphia, PA 19104
Enrolling Participants:	200 participants will be enrolled
Description of Study Intervention:	Genetic: 16 PGx gene panel (*CYP2B6, CYP2C19, CYP2C9, CYP2C Cluster, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-A, HLA-B, IFNL4, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1*) The study utilizes a lab developed test (OneOme, Minneapolis, MN) performed in a CAP and CLIA accredited environment that provides identification of a patient's genotype determined from genomic DNA from a buccal sample with a turnaround time of 7-10 business days after receiving the sample. This is a randomized, prospective, open-label study. Patients with planned gynecologic surgeries will be randomized to the PGx-guided group or the control group (usual care). Following consent, the surgeon will place a PGx test order; the buccal sample will be collected by the participant and mailed to OneOme for genotyping. Results will be returned electronically to the EMR (PennChart). The results will appear in the EMR when available for those in the PGx-guided group and delayed by approximately 30 days post-surgery for those in the control group. A pharmacist will review the results for the PGx-guided group and create/send a consult note to the surgeon with recommendations for analgesia based on the PGx results and other clinical factors (e.g., renal/hepatic function, drug allergies, age, drug interactions, comorbid conditions, etc.). Additionally, for participants with an actionable genotype (variants that would require a dose adjustment or therapeutic alternative of an analgesic), clinical decision support (CDS) tools will

	alert the ordering surgeon of the PGx result and the recommended dose adjustment or need for an alternative therapy. The prescribing surgeon will ultimately decide the analgesic regimen incorporating the pharmacist recommendations and other relevant clinical factors. A pharmacist will create/send a detailed letter to the patient and their primary care provider explaining the patient's PGx test results for both cohorts.
Study Duration:	Two years
Participant Duration:	1 year

1.2 Key Roles and Study Governance

Sponsor: **University of Pennsylvania**
Sony Tuteja, PharmD, MS Research Assistant Professor of Medicine Assistant Director, Pharmacogenomics, Penn Center for Precision Medicine
Institution Name: University of Pennsylvania Perelman School of Medicine Department of Medicine Division of Translational Medicine and Human Genetics
Address: Smilow Center for Translation Research 3400 Civic Center Blvd, 11-142 Philadelphia, PA 19104-6160
Phone Number: 484-431-1002
Email: sonyt@pennmedicine.upenn.edu

1.3 Schema


Total 200: Screen potential participants by inclusion and exclusion criteria. Obtain informed consent.
Randomize
PGx-guided group n=100
Control group (usual care) n=100
PGx buccal swab is collected by participant in office. Sample mailed to OneOme by office staff.
PGx buccal swab is collected by participant in office. Sample mailed to OneOme by office staff.
PGx results returned to the genomics portal and released to the EMR in 7-10 days. A pharmacist reviews PGx results & creates a consult note with genotype-guided medication recommendations. CDS will alert ordering provider at time of prescribing of dose adjustments or need for alternative analgesic.
Participant gynecologic surgery: Surgeon will decide analgesic regimen based on relevant clinical factors.
Participant gynecologic surgery: Surgeon will decide analgesic regimen; incorporating the pharmacist recommendations and other relevant clinical factors.
PGx results returned in genomics portal in 7-10 days. Results will not be released to the EMR until approximately 30 days after surgery.
A pharmacist will create/send a detailed letter to the patient and their primary care provider explaining the patient's PGx test results.
Endpoints collected prospectively:
refer to **Appendix Section 13.1, Schedule of Activities**

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

There are known PGx variants in *CYP2C9* and *CYP2D6* genes associated with efficacy and safety of certain opioid medications and NSAIDs.[1,2] Testing for these variants in patients with acute postoperative pain is not routinely performed and it is unknown whether this testing can decrease overall opioid consumption in these patients without compromising pain control. Prior studies of *CYP2D6* genotyping in patients with chronic pain or acute post-op pain have shown promising results.[3,4] We will conduct a randomized, open-label, pilot implementation study to determine the feasibility of integrating a preemptive PGx test using a multi-gene panel into clinical care along with a pharmacist consult to provide patient specific analgesic recommendations and dosing in post-op gynecologic surgery patients. Effectiveness of the PGx-guided approach will be determined by comparing, in variant carriers, the numeric pain scores, total opioid consumptions as assessed by daily morphine milligram equivalents (MME), and incidence of opioid/NSAID-related ADRs to a control group receiving usual care. The use of a preemptive 16 gene PGx panel is important for our tertiary endpoint to collect the number of additional CPIC Level A and B drugs prescribed in the year following surgery to understand the reusability of the multi-gene panel for all providers. Preemptive PGx testing is further discussed below in section 2.2.

2.2 Background

Gynecologic surgeries are among the most commonly performed operating room procedures in the U.S. and cause varying levels of acute postoperative pain.[5] Uncontrolled pain can lead to decreased quality of life, increased morbidity (e.g., compromised sleep, nausea, vomiting, anxiety, etc.), and chronic postoperative pain.[6] Opioids and NSAIDs are commonly used to treat postop pain.[7] Efficacy and toxicity of opioid pain medications including codeine, tramadol and hydrocodone are impacted by *CYP2D6* variants.[1] While *CYP2C9* variants help to predict an individual's risk for ADRs for certain NSAIDs such as ibuprofen and meloxicam.[2]

The CYP2D6 enzyme metabolizes codeine and tramadol to their respective active metabolites, morphine and *O*-desmethyltramadol.[8] In individuals with 1 or 2 copies of decreased or no function alleles (i.e. CYP2D6 intermediate metabolizers [IM] or poor metabolizers [PM]), morphine and *O*-desmethyltramadol formation is decreased, resulting in poor pain control.[1] Conversely, those with copy number variations (CNV) in CYP2D6 (i.e. ultra-rapid metabolizers [UM]) have an increased conversion to the active metabolite resulting in a higher incidence of opioid related toxicity including nausea and respiratory depression.[1] NSAIDs are also commonly recommended for intraoperative and post-op pain management to minimize opioid use but are also associated with risk of severe ADRs, such as gastrointestinal inflammation, ulcers, or hemorrhage; acute kidney injury; acute myocardial infarction; cerebrovascular accidents; hyperkalemia.[7,9,10] PGx testing can predict an individual's risk for ADRs and subsequently guide dosing and selection of NSAIDs by detecting variations in the *CYP2C9* gene.[2]

Other factors such as age, comorbid conditions, renal/hepatic function, concomitant medications, phenoconversion, etc. can also influence medication metabolism. Phenoconversion occurs when non-genetic factors influence an individual's ability to metabolize medications (phenotype), causing a mismatch with the genotype predicted drug metabolism.[11] Phenoconversion can occur from drug-drug interactions, particularly with concomitant use of strong inhibitors of the cytochrome P450 enzymes (e.g. CYP2D6 strong inhibitors → bupropion, fluoxetine, paroxetine).

CYP2D6 and *CYP2C9* results can be applied in clinical practice by using peer-reviewed, evidence-based guidelines provided by the NIH-funded Clinical Pharmacogenetics Implementation Consortium (CPIC) (Table 1).[1,2] Alternatives to codeine and tramadol are recommended for analgesia in CYP2D6 UMs and PMs,[1] and dosing recommendations for codeine, tramadol, and hydrocodone are suggested for CYP2D6 IMs and PMs.[1] Similarly, alternatives and/or dose adjustments to celecoxib, flurbiprofen, ibuprofen, meloxicam, and piroxicam are recommended for CYP2C9 IMs (Activity Score [AS] 1) or PMs.[2]

Table 1. Pharmacogenes associated with pain medication treatment

Gene	Phenotype	Phenotype frequency*		Affected Drugs	Effect on drug
		EU	AA		
CYP2D6	UM	0.031	0.045	Codeine, tramadol	Increased risk of toxicities
	IM	0.39	0.36	Codeine, tramadol	Decreased response
	PM	0.065	0.023	Codeine, tramadol	Decreased response
	IM or PM	0.45	0.39	Hydrocodone	Possible decreased response
CYP2C9	IM (AS 1)	0.138	0.05	Celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam	Increased risk of toxicities
	PM	0.026	0.005	Celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam	Increased risk of toxicities and/or severity of toxicities

* Frequencies per Clinical Pharmacogenetics Implementation Consortium (CPIC); AA: African ancestry; EU: European ancestry; AS: activity score; UM: ultrarapid metabolizer; IM: intermediate metabolizer; PM: poor metabolizer

Previous work in this area includes a pragmatic, non-randomized, open-label, prospective, cluster design study comparing *CYP2D6* genotype-guided opioid treatment to usual care in 375 patients with chronic pain.[3] Pharmacists suggested alternative analgesics after reviewing the PGx results and assigning a CYP2D6 phenotype using activity scores and drug-induced phenoconversion for interacting concomitant medications. Hydrocodone or morphine was suggested for UM, PM, and IM (only where pain was uncontrolled with codeine, hydrocodone, oxycodone, or tramadol). They found a significant difference in the number of CYP2D6 IMs and PMs, who were receiving tramadol or codeine prior to study enrollment, with a 30% decrease in composite pain intensity in the CYP2D6-guided group compared to usual care group.

Another randomized, open-label, type 2 hybrid implementation-effectiveness study evaluated CYP2D6-guided opioid selection in 260 post-op hip or knee arthroplasty patients.[4] Similarly, a pharmacist provided analgesic recommendations based on the participant's CYP2D6 phenotype. Tramadol was recommended opioid for CYP2D6 NMs and hydromorphone, morphine, or non-opioid was recommended for CYP2D6 IMs, PMs, or UMs. They found that pain intensity was similar in the CYP2D6-guided group compared to the usual care group. However, the total MME in the CYP2D6-guided group was significantly lower compared to the usual care group.

One strategy for testing PGx variants is by preemptive panel testing or testing for multiple actionable pharmacogenes in anticipation of potential future drug-gene interactions (DGIs).[12] Initial findings indicate that preemptive panel testing is cost-effective compared to reactive panel testing (i.e. testing multiple genes at the time of or after initiating a high-risk medication) and it is hypothesized that overall cost-effectiveness with the preemptive testing model increases over time.[13] In a study conducted at the Veteran Health Administration (VHA) evaluating pharmacy records for over 7 million Veterans over a 6-year period, 54.8% were prescribed at least one drug with a DGI, 15.3% received two, and 11.7% receive 3 or more drugs.[14] This study demonstrates that patients are prescribed multiple drugs with DGIs over a relative short period of time and the reusability of the PGx panel.

Integration of PGx results in the EMR along with CDS tools to provide genotype-guided medication recommendations at the point of prescribing is a crucial component to enhance adoption of clinical PGx testing.[15,16] While EMR-based tools are vital for widespread PGx adoptions, EMR based provider alerts are notorious for being ignored, as evidenced by a study of drug-drug interaction alerts, where 93% were overridden or ignored.[17] This is somewhat improved for PGx alerts. A study evaluating PGx alerts in 6 sites published by the Electronic Medical Records and Genomics (eMERGE) consortium, described wide variation in acceptance and follow rates with 26% of alerts overridden and 12% ignored resulting in clinical responses followed in 42% of cases.[16] It may be that application of PGx results cannot be accomplished in certain situations without detailed knowledge of individual patients, their clinical condition, ongoing therapy, and the recognition of the multiple factors that can influence therapeutic response such as phenoconversion. The addition of an consult by a pharmacist will allow for a more patient-specific recommendation by taking into account additional patient factors.[18] A recent study found that by adding a pharmacist consult in addition to the general PGx information included in the PGx lab report, recommendations could be streamlined to only include those directly impacting the patient's current care.[18] In addition, the pharmacists included genotype-guided medication recommendations for untreated conditions that were not included in the PGx lab report.[18]

Genotyping for this study will be performed by the 16-gene PGx panel from OneOme which is already in use for patients seen in the PGx clinic through Medical Genetics. The electronic interface with OneOme went live in October 2021, and the results appear as discrete components, which will streamline the ordering and resulting process for gynecologic clinicians. We have worked with the PennChart (Epic) informatics analysts at Penn Medicine to build CDS in the EMR for all DGIs with CPIC level A and B guidelines, except for the following genes:

CYP2C cluster, CYP4F2, and VKORC1, which is in progress. The CDS provides guidance for medication selection and dosing based on PGx results and will be available to all Penn Medicine providers during the study period and after the study has ended. The cost of the panel test is equivalent to single gene tests.

2.2.1 *Description of intervention*

This study utilizes a preemptive testing approach with a PGx panel that tests for 16 CPIC Level A pharmacogenes (*CYP2B6, CYP2C19, CYP2C9, CYP2C Cluster, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-A, HLA-B, IFNL4, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1*) from a buccal sample provided and resulted by a CAP and CLIA accredited genotyping lab (OneOme, Minneapolis, MN) (See section 6.1.1 Study Intervention Description).

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The risk associated with self-collection of a buccal swab is minimal.

There can be a risk in knowing genetic information. New health information about inherited traits that may affect participating patients and or their blood relatives may be found during the research study. Most PGx results are not associated with incidental findings except for UGT1A1. These diseases are typically identified at birth or in early childhood[19,20] and therefore PGx testing is unlikely to result in these incidental findings:

UGT1A1 plays a role in the metabolism of bilirubin and is associated with hereditary hyperbilirubinemia syndromes. The **28* variant is a common cause of Gilbert syndrome.[19] Individuals with Gilbert syndrome may experience transient elevations in unconjugated plasma bilirubin in response to various triggers (e.g., fasting, infection, or medications). Genotypes most implicated in Gilbert syndrome are UGT1A1*28/*28 and UGT1A1*6/*6.[19] Crigler-Najjar syndrome type I is very rare and results from deleterious UGT1A1 mutations that results in hyperbilirubinemia[19] and occur early in childhood therefore the PGx testing is unlikely to result in incidental findings. However, identification of a heterozygous state may have implications for prenatal genetic counseling.

Incidental findings will be communicated to the patient through the detailed note (appendix section 13.7) and to the patient's primary care physician (PCP) (if participant identifies a PCP and wants the letter to be sent). If the patient has additional questions, they can be referred to a genetic counselor.

Additionally, there is the risk of loss of privacy with storing the health and genetic data of participating patients. Very rarely health or genetic information could be misused by employers or insurance companies; however, in such events, patients may have difficulty finding or maintaining a job or insurance. Laws such as the federal Genetic Information Nondiscrimination Act (GINA) prohibit employers and health insurers from discriminating against

individuals based on their genetic information. However, GINA does not protect against life insurance or long-term care insurance.

2.3.2 Known Potential Benefits

The potential benefit to the study participants is having their analgesic regimen tailored to their genetic profile so as to avoid medication-related toxicities and/or lack of efficacy.

2.3.3 Assessment of Potential Risks and Benefits

The study is considered low risk since the medications of interest in the study are FDA-approved for clinical use for analgesia. The study will provide valuable information on the best methods for incorporation PGx testing into clinical care to improve efficacy and decrease adverse events.

3 STUDY OBJECTIVES AND ENDPOINTS

Hypothesis:
The availability of a multi-gene PGx panel test with a pharmacist consult will increase PGx test utilization, provide tailored pain medication recommendations, and improve patient outcomes.

OBJECTIVES	ENDPOINTS
Primary	
1. To determine the feasibility of integrating a PGx panel test in the EMR with a pharmacist PGx consult for each patient. 2. Determine the fidelity to genotype-guided pharmacotherapy recommendations.	1. The proportion of PGx test results and consults returned prior to surgery. 2. The proportion of dose modifications and medication selections made in agreement with the genotype-guided dosing recommendations for analgesic medications.
Secondary	
1. To determine if PGx testing will improve the patient self-reported numeric pain scores in patients 2. To determine if PGx testing will decrease ADRs resulting from the opioid pain regimen. 3. To determine if PGx testing will decrease ADRs resulting from the NSAID pain regimen in participants with actionable CYP2C9 variants. 4. To determine if PGx testing will decrease the total opioid consumption. 5. To assess provider attitudes toward PGx testing. 6. To assess patient attitudes towards PGx testing.	1. Mean patient self-reported numeric pain scores (POD 0, 1, & 2 (only while admitted) and POD 3, 7, & 14 in variant carriers in the PGx-guided group vs. control group. 2. Number of opioid-related ADRs in the PGx-guided group vs. control group 3. Number of NSAID ADRs in variant carriers in the PGx-guided group vs. control group 4. The difference in total MME consumption in the PGx-guided group vs. control group (POD 0-7 and POD 1-14). 5. Baseline provider attitudes toward and knowledge of PGx testing as assessed by a questionnaire. 6. Patient experience with PGx testing at 30 days after surgery as assessed by a questionnaire.
Tertiary	
1. To determine if PGx testing is associated with a decreased hospital LOS. 2. To determine population frequency of PGx variants 3. To determine reusability of the multi-gene panel 4. To determine if PGx testing impacts chronic use of opioids.	1. Length of hospital admission in the PGx-guided group vs. control group. 2. Minor allele frequencies of CYP2D6 and CYP2C9 actionable variants by ancestry. 3. Number of additional CPIC Level A and B drugs prescribed in the year following surgery and number of EMR alerts fired to non-gyn surgery providers. 4. Number of participants on chronic opioids at 6 months and at 1 year.

4 STUDY PLAN

4.1 Study Design

This is a single site, randomized, prospective, open-label pilot implementation study to determine the feasibility of integrating a PGx testing into clinical care. The effectiveness of the PGx-guided approach will be determined by comparing the numeric pain scores, overall opioid consumptions as assessed by total MME, and incidence of opioid/NSAID-related ADRs to a control group (usual care).

Once enrollment is open, patients seen at any of the practice sites for surgical consultations, will be evaluated by their treating physician for eligibility based on the planned gynecologic surgery. Study staff will screen and identify patients for enrollment with the assistance of the treating physician. The study will be discussed with the patient to determine their interest. If the patient agrees to participate, they will be consented by their physician or study staff and randomly assigned to the intervention group (PGx-guided) or the control group (usual care). In the case where surgical intervention is likely, but not definite at the initial surgical consultation visit, once surgery is confirmed, study staff will contact the patient via phone to discuss participation in the study. Consent will be collected through My Penn Medicine (MPM) if the patient is enrolled or verbally if not enrolled in MPM and a copy of the consent will be emailed to the participant.

The PGx test panel order will be signed by a surgeon; a buccal swab kit will be provided to the patient for self-collection; the test kit will be returned to OneOme by the office, research staff, or the participant if collected outside of the clinic visit. The results will be returned electronically in the Precision Medicine tab in PennChart after they are released from a result portal by study personnel.

For the intervention group (PGx-guided group): The results will be released from the result portal within one business day from the day they are available in the portal for release. A pharmacist will review the results and create a consult note within 3 business days with analgesic medication selection and dose recommendations based on actionable genotypes and other clinical factors (e.g., renal/hepatic function, drug allergies, age, drug interactions, comorbid conditions, etc.). A pharmacist will create/send a detailed letter to the patient and their primary care provider explaining the patient's PGx test results. CDS tools will alert providers of actionable genotypes and include recommendations for dosing or medication selection at the time of ordering an affected medication. The prescribing surgeon will ultimately determine analgesic selection and dosing.

For the control group (Usual care group): The prescribing surgeon will order analgesic medications based on usual, standard of care practices. The results will be released from the result portal approximately 30 days after the participant's surgery. A pharmacist will create/send a detailed letter to the patient and their primary care provider explaining the patient's PGx test results. The control group (usual care) will receive PGx testing, but not receive the results for 30 days. This is to allow us to compare the effectiveness of the PGx-guided approach to those who

received usual care and were variant carriers. Holding results for 30 days is justified because doing this testing in clinical practice is not yet standard of care.

To ensure that pharmacogenetic results are released to the patient, if surgery is not scheduled within 9 months after study enrollment, the pharmacogenetic results will be released to the EHR and the patient regardless of the study arm group they are assigned.

For both groups, participants will receive two-way text messaging (via RedCap using Twilio as the SMS service) after discharge from the hospital on POD# 3, 7, and 14 to collect self-reported measures (see Section 7.6 and 13.9 for further details).

The detailed letter to the patient and their primary care provider includes how to contact the PGx pharmacist for questions regarding their results. A pharmacist consult is available to study participants at no charge. If consult with a genetics provider is requested (Genetics physician or genetic counselor) they may be referred to the Medical Genetics clinic for an appointment, fees associated with this consult will be the responsibility of the patient.

4.1.1 Medication selection and dose recommendations based on genotype

Genotype-guided medication selection and dose recommendations will be made according to peer-reviewed, evidence-based clinical practice guidelines from CPIC and patient clinical factors (e.g., renal/hepatic function, drug allergies, age, drug interactions, comorbid conditions, etc.). (See section 13.4 & 13.5 for analgesic medication selection and dosing algorithm)

4.2 Scientific Rationale for Study Design

This is primarily a pilot implementation study to determine the feasibility of incorporating a preemptive PGx panel test into the gynecological surgery workflow. The randomized approach will help provide effect estimates for the relationship of the PGx testing on effectiveness (i.e., patient reported numeric pain score, MME, and ADEs).

5 STUDY POPULATION

5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Able and willing to provide informed consent
2. Assigned female at birth and aged 18 years or older at the time of study initiation
3. Major gynecologic surgery indicated and planned for hysterectomy, myomectomy, exploratory laparotomy, and open abdominal surgery
4. Willing to provide a buccal swab for PGx testing and comply with all study-related procedures

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Receiving chronic opioid therapy defined as ≥ 3 consecutive months of 1-month prescriptions for an opioid.
2. Pregnancy (per standard care, all patients will receive a urine pregnancy test pre-operatively on the day of surgery. If pregnancy is not reasonably excluded during the preoperative evaluation visit a pregnancy test will be collected at that time)
3. Breastfeeding (tramadol is not the preferred opioid in breastfeeding women)
4. Treating physician does not want subject to participate

5.3 Screen Failures

Screen failures in this study will be defined as participants who meet criteria for enrollment but decline to participate or the treating surgeon declines participation of their patient in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

5.4 Strategies for Recruitment and Retention

The surgeon will discuss the study with the patient during the surgical evaluation visit and consent will be obtained by the surgeon, designated clinical staff, or study staff. This will occur in person. Participants will be given a copy of the official informed consent form and an opportunity to ask questions. Study staff will identify eligible patients scheduled for surgery in the following month who have not been approached about the study. Study staff will contact the patient via phone to discuss participation in the study, if interested, consent will be collected through My Penn Medicine (MPM) if the patient is enrolled or verbally if not enrolled in MPM and a copy of the consent will be emailed to the participant.

Participants will be given a Greenphire ClinCard (reloadable debit card) for completing certain steps in the study. A total of $10 will be added to the Greenphire ClinCard after completing all of the text message questionnaires ($3.33 for each of the first 2 text message questionnaires and $3.34 for the 3rd text message questionnaire, totaling $10). An additional $15 will be added to the Greenphire ClinCard for completing the patient survey approximately 30 days after their surgery. The Greenphire ClinCard is a virtual card that will be emailed to the participants.

5.5 Duration of study participation

Total involvement for each participant will be from the time of consent (at surgical evaluation visit) to 14 days post-op. Participants will be sent a survey to complete 30 days post-op (not

likely to exceed 2 months total). Data will be collected from the EMR up to 1 year after PGx test pertaining to medications prescribed to participants.

5.6 End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study shown in the Schedule of Activities (SoA), Section 13.1.

6 STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 *Study Intervention Description*

This study utilizes PGx testing for 16 pharmacogenes (*CYP2B6, CYP2C19, CYP2C9, CYP2C Cluster, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-A, HLA-B, IFNL4, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1*) from a buccal sample provided and resulted by a CAP and CLIA accredited genotyping lab (OneOme, Minneapolis, MN). This test does not detect all known and unknown variations in the genes tested. Reporting a *1 is indicative of no variations based on the below alleles reported.

The following alleles will be identified:

Table 2. Gene details of OneOme panel test

Gene	rsID	Alleles Reported
CYP2B6	rs3745274	*6, *7, *9
	rs28399499	*16, *18
	rs2279343	*4, *6, *7, *16
	rs3211371	*5, *7
CYP2C19	rs4244285	*2
	rs4986893	*3
	rs12248560	*4B, *17
	rs28399504	*4, *4B
	rs6413438	*10
CYP2C9	rs1799853	*2
	rs1057910	*3
	rs1057911	*3
	rs56165452	*4
	rs28371686	*5
	rs9332131	*6
	rs7900194	*8
	rs28371685	*11
CYP2C Cluster	rs12777823	rs12777823 GG rs12777823 GA

		rs12777823 AA
CYP2D6		*5, *18, *34, *39, *59, *61, *65, copy number variations
	rs1080985	*2A, *11, *14, *31, *35, *63
	rs769258	*35
	rs1065852	*4, *4J, *4N, *10, *36, *64, *68, *69, *114
	rs5030862	*12
	rs201377835	*11
	rs5030865g>t	*8
	rs5030865g>a	*14, *114
	rs5030656	*9, *109
	rs28371706	*17, *64
	rs5030655	*6, *6C
	rs3892097	*4, *4J, *4K, *4M, *4N
	rs35742686	*3
	rs5030867	*7
	rs59421388	*29. *70, *109
	rs28371725	*41, *69, *91
	rs16947	*2, *2A, *8, *11, *12, *14, *17, *19, *29, *31, *35, *41, *42, *63, *69, *91, *114
	rs1135840	*2, *2A, *4, *4N, *6C, *8, *10, *11, *12, *14, *17, *19, *29, *31, *35, *36, *41, *42, *64, *69, *70, *114
	rs267608319	*31
	rs774671100	*13, *15
	rs72549353	*19
	rs72549346	*42
	hCV32407220 (rs765776661)	*18
	rs79292917	*59
CYP3A5	rs776746	*3
	rs10264272	*6
	rs41303343	*7
CYP4F2	rs2108622	*3
DPYD	rs3918290	*2A
	rs67376798	c.2846A>T (p.Asp949Val)
	rs55886062	*13
HLA-A	HLA00097	*31:01 (Negative/Positive)
HLA-B	rs144012689	*15:01 (Negative/Positive)
	HLA00381	*57:01 (Negative/Positive)
	HLA00386	*58:01 (Negative/Positive)
IFNL4 (IL28B)	rs12979860	rs12979860 CC rs12979860 CT

		rs12979860 TT
NUDT15	rs116855232	rs116855232 CC rs116855232 CT rs116855232 TT
SLCO1B1	rs4149056	*5, *15, *17
	rs4149015	*15, *21
	rs2306283	*1B, *15, *17, *21
TPMT	rs1800462	*2
	rs1800460	*3A, *3B
	rs1142345	*3A, *3C
	rs1800584	*4
UGT1A1	rs4148323	*6
	rs1976391	*28(TA7)
VKORC1	rs9923231	rs9923231 GG rs9923231 GA rs9923231 AA
	rs7200749	rs7200749 GG rs7200749 GA rs7200749 AA

6.1.2 *Dosing and Administration*

Analgesic selection and dosing recommendations will be based on the participant's CYP2C9 and CYP2D6 genotype and other clinical factors as indicated in the algorithms found in Section 13.4 and 13.5. Final medication selection and dosing will be determined by the treating surgeon according to their best clinical judgement.

6.2 Study Intervention Compliance

Compliance to the PGx testing will be determined by tracking the test orders in PennChart. Study team will record the date/time of sample collection, time of sample receipt at OneOme Labs, and time of results posted in PennChart. Test turnaround time will be calculated, using the date of the order as the sample collection date to the time the results are populated in PennChart through an electronic interface from OneOme.

6.3 Discontinuation of Study Intervention

If the participant withdraws from the study after the buccal swab has been processed by OneOme, the PGx test results will remain in the EMR, but no further data will be collected related to the research study endpoints.

6.4 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request, without prejudice to their medical care, and are not obliged to state their reasons. The study investigator may discontinue or withdraw a participant from the study for the following reasons:

- Treating surgeon wishes patient to withdraw
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant transfers care outside of Penn Medicine

The reason for participant discontinuation or withdrawal from the study will be recorded on the participant's Case Report Form (CRF). Subjects who sign the informed consent form but do not undergo genotyping may be replaced. Subjects who sign the informed consent form and are randomized to undergo genotyping, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.5 Lost to Follow-Up

A participant will be considered lost to follow-up if she fails to return for scheduled gynecologic surgery. There are no study-specific visits. Data is collected at the time of clinic visit (gynecologic surgical evaluation), gynecologic surgery-related hospitalization, from the medical record (EMR), and/or through text messaging.

The following actions must be taken if a participant fails to return for gynecologic surgery:

- The investigator will contact the surgeon to determine the reason for not returning for gynecologic surgery.
- If the patient wishes to discontinue from the study, an attempt will be made to establish the reason for discontinuation (bearing in mind that the participant is not obligated to share her reasons).

7 STUDY ASSESSMENT AND PROCEDURES

7.1 Provider on attitudes toward and knowledge of PGx testing (Baseline)

Surgeons, including surgery residents and fellows, will be sent an optional electronic survey via an emailed link in RedCap to assess their knowledge and attitudes toward pharmacogenetic testing prior to receiving education about the study (see appendix 13.10). A paper copy will be made available for those without computer access.

Surgeons, including surgery residents and fellows that practice at Jordan Center for Gynecologic Cancers at PCAM, Penn Health for Women Radnor, Penn Ob/Gyn Associates, Penn Health for Women University City, or Helen O. Dickens Center for Women's Health at Hospital of the University of Pennsylvania will be asked to complete an electronic survey to assess their knowledge and attitudes toward pharmacogenetic testing prior to or shortly after receiving education about the study (see appendix 13.10).

7.2 Provider education

After the survey is administered and completed, the study PGx pharmacist will conduct educational sessions for the physicians that includes background information about PGx testing, an introduction to PGx testing services currently available to the health system, and details pertaining to the PRECISE research study.

7.3 Screening and identification

Study staff will screen and identify patients for enrollment with the assistance of the treating physician.

7.4 Informed consent

Consent forms describing in detail the PGx test, study procedures, and risks are given to the participant. Participants will also receive an educational brochure about the purpose of PGx testing and what to expect with return of results. The informed consent signature will be collected electronically by the physician, study staff, or surgical coordinator through PennChart (Epic) or using a paper copy. A copy of the informed consent document will be given to the participants for their records either electronically via My Penn Medicine (MPM) or a paper copy Eligible patients not identified in the clinic, who are eligible, will be identified by the surgical residents and contacted via phone by study staff to discuss participation in the study. Consent will be collected through My Penn Medicine (MPM) if the patient is enrolled or verbally if not enrolled in MPM and a copy of the consent will be emailed to the participant.

7.5 Randomization

The block randomization schema will be designed by the Clinical Research Computing Unit (CRCU) in REDCap. Randomization will be stratified based on age (<65 or ≥65 years), clinic

location (PCAM or Dickens clinic), and gynecologic surgery type (minimally invasive vs. open laparotomy). Surgeon will log-in to REDCap to receive the group assignment: 1) PGx-guided (active) vs. 2) usual care (control).

7.6 Genotyping (Baseline)

A surgeon will sign an order for the PGx test in PennChart during the surgical evaluation appointment. Buccal swab sample collection via OneOme test kit will be self-collected by the participant after study consent at this same visit or a collection kit will be sent to the participants home for participants consented verbally or electronically outside of a clinic visit. Collection of the buccal sample must occur at least 30 minutes after eating, drinking, smoking, or chewing gum. The participant will remove the collector swab from the packaging without touching the sponge tip to any surface. They will place the swab on one side of their mouth on their lower gums and swab back and forth 10 times. They will then switch the swab to the other side of their mouth and swab 10 more times. The swab will then be inserted into the provided tube and shaken 10 times. If the sample is collected during the office visit, it will be mailed to OneOme by study staff. If the sample is collected by the participant at home, the participant will mail the kit to OneOme.

7.7 Clinical data collection (Baseline)

The following information will be obtained at screening or from the patient medical record:

- Signed informed consent
- Inclusion and exclusion criteria
- Randomization
- Name, address, telephone number, date of birth, email (if available)
- Demographic data: age, race/ethnicity (if available), gender
- Medical record number
- Smoking history (if available in the EHR)
- Diagnosis prompting surgical consultation
- Prior medical history including history of chronic pain medication use
- Routine physical examination: height, weight (if available from surgical evaluation)
- Clinical chemistry: creatinine, AST, ALT (Only if available within 30 days prior to the scheduled surgery. These labs will not be ordered specifically for this study.)
- Creatinine clearance (using Cockcroft-Gault formula) if creatinine is available within 30 days prior to scheduled surgery.
- Concomitant medications collected via medical record if available (including the following information if documented in the medical chart: dose, unit, frequency, route of administration and indication)

7.8 Return of pharmacogenetic results

A pharmacist will review the PGx results from OneOme through the MedView portal.

For the PGx-guided group: The PGx results will be released from the portal to Epic. A consult note will be created and sent to the surgeon, including recommendations for post-operative analgesia based on the PGx results (see appendix section 13.8). A detailed note outlining recommendations for all PGx results will be created and sent to the participant and their PCP (if participant identifies a PCP and wants the letter to be sent) (see appendix section 13.7).

For the Usual care group: The PGx results will be released from the portal to Epic approximately 30 days after surgery. A detailed note outlining recommendations for all PGx results will be created and sent to the participant and their PCP (if participant identifies a PCP and wants the letter to be sent) approximately 30 days after surgery (see appendix section 13.7).

7.9 Implementation metrics (0-30 days)

The following information will be collected to determine feasibility of PGx test implementation and agreement to the PGx-guided dosing recommendations:

- Dates of sample collection, date of result transfer into PennChart, date of pharmacist consult note within PennChart, and date of gynecologic surgery
- Analgesic(s) selected, and dose prescribed
- Reasons for not adhering to the PGx guided recommendations if applicable
- The number of actionable variants for each patient
- Number of medication orders that align with PGx-guided dosing recommendations

7.10 Data collection after surgery (0 to 2 months)

Collected from review of the medical record (EMR) during hospitalization (POD 0-2):

Data will not be collected for POD 1-2 if the subject has been discharged.

- Daily average numeric pain score (using a 0-10 numeric scale)
- Name, dose, units, and number of doses of pain medication taken
- Daily calculated MME for all opioids administered
- Naloxone administration (including dose, date/time of administration)

Collected via two-way text messaging via REDCap using Twilio as the SMS service:

Text messages will only be sent to discharged subjects. The following data will be collected via review of EMR if the subject is hospitalized during these time points.

- Daily average numeric pain score (using a 0-10 numeric scale) on POD 3, 7, & 14

- The total number of doses of pain medication taken (including total calculated MME for timeframe) post-discharge to POD 3, POD 4-7 (assessed on day 7), and POD 8-14 (assessed on day 14).The total number of tablets/capsules remaining in their prescription bottle on POD 3, 7, & 14

Collected from EMR after discharge

- Prescriptions (including dose and units) for any new pain medication prescribed within 30 days of the procedure
- Adverse drug reactions to analgesic regimen (collected from the EMR from chart review either during hospitalization or through other encounter notes in the EMR)

7.11 Patient survey on knowledge and satisfaction of PGx testing (30 days post-study)

Patients will complete an electronic survey via an emailed or texted link from RedCap to assess their knowledge and satisfaction of pharmacogenetic testing (see appendix 13.11). A paper copy will be made available for those without computer access.

7.12 Data collected from medical records (EMR) (1 year)

The following information will be collected up to 1-year post-surgery through review of the medical record (EMR):

- Number of additional CPIC level A and B medications prescribed
- Number of CPIC level A and B medications prescribed that align with PGx-guided recommendations

8 SAFETY AND ADVERSE EVENTS

8.1 Adverse Events and Serious Adverse Events

8.1.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. AEs in clinical investigation will include those associated with the study intervention (the PGx test). Adverse drug reactions (ADRs) associated with analgesic treatment will be collected as study outcomes, not as study-related adverse events.

Anticipated AEs may include incidental findings related to PGx test results and the sharing of information to patients (refer to section 2.3.1).

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

8.1.3 Classification of an Adverse Event

AEs in clinical investigation will include AEs associated with the PGx test since the analgesic medications that will be administered are standard of care. These will primarily be related to HIPAA issues and unexpected findings.

8.1.3.1 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to the PGx test assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Related – The AE is known to occur with the PGx test, there is a reasonable possibility that the PGx test caused the AE, or there is a temporal relationship between the PGx test and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the PGx test and the AE.
- Not Related – There is not a reasonable possibility that the administration of the PGx test caused the event, there is no temporal relationship between the PGx test and event onset, or an alternate etiology has been established.

8.1.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by study personnel at the time of PGx test resulting. Analgesic adverse events described in section 8.1.2 will be documented.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Description of adverse event
2. Date of occurrence
3. Analgesic and other medications administered within 24 hours prior to the adverse event (for analgesic adverse events only)
4. Expectedness to study intervention (PGx test) – Unexpected (yes/no)
5. Impact on patient care – patient informed (yes/no)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made of any changes in patient care.

8.1.5 Adverse Event Reporting

AEs encountered during the study will be documented in the patient's file and reported on the Case Report Form (CRF). Likelihood of the AE being attributed to the PGx test will be documented.

The information that will be recorded in the patient's file consists of"

- Description of the event
- Date of the event
- Impact on patient care

Reporting to the IRB will be done in accordance to the *Penn IRB definition of reportable events and reporting timelines*.

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

8.1.6 Serious Adverse Event Reporting

A SAE must be reported to the study investigator by telephone within 24 hours of the event. The investigator will keep a copy of this form on file at the study site. Report SAEs by phone to:

Glenda Hoffecker, PharmD
Mobile: (484) 678-0732

In the event that Dr. Hoffecker cannot be reached, report SAEs to:

Sony Tuteja, PharmD
Mobile: (484) 431-1002

Mary Deagostino-Kelly, MD

Mobile: (215) 900-5494

At the time of the initial report, the following information should be provided:

- Study name
- Participant number
- A description of the event
- Date of onset
- Current status
- The reason the event is classified as serious
- Investigator assessment of the association between the event and the PGx test

Within the following 48 hours, the investigator must provide further information on the SAE in the form of a written narrative. Significant new information on ongoing SAEs should be provided promptly to the study investigator.

Reports of all SAEs (including follow-up information) must be submitted to the IRB within 10 working days, unless the SAE involves a death, which must be reported within 3 days. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.2 Unanticipated Problems

8.2.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Breach of confidentiality
- OneOme is unable to provide genotyping

should be reported by the investigator to the Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.
- Any other UP will be reported to the IRB within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL PLAN

9.1 Sample Size

For the implementation aims, the sample size is based on average gynecologic surgery volume and anticipated number of patients that are eligible for testing. We anticipate enrolling 200 patients in 1 year. No hypothesis testing will be performed.

9.1.1 Populations for Analyses

We will evaluate effectiveness outcomes between the PGx-guided group and usual care group.

9.2 Statistical Analyses

9.2.1 General Approach

Descriptive statistics mean, SD, median, range, counts, and percentages will be used to describe and compare (t-test or rank sum test for continuous variables and Fisher's exact test for

categorical variables) baseline characteristics between the PGx-guided group and the usual care group.

9.2.2 Analysis of the Primary Endpoint(s)

Implementation Endpoint(s):

a) We will report the number and proportion of tests returned prior to the gynecologic surgery day.

b) We will report the proportion of medication selection and dose modifications made in agreement with the pharmacist genotype-guided recommendations.

9.2.3 Analysis of the Secondary Endpoint(s)

Clinical endpoints:

a) The proportion of participants achieving at least a 30% reduction in pain scores will be compared in the PGx-guided group vs. the control group using Fisher's exact test.
b) The mean patient self-reported numeric pain scores (POD 0, 1, 2 (only while hospitalized) and POD 3, POD 7 and 14 will be compared in the PGx-guided group vs. the usual care group using t-test.
c) The change in mean patient self-reported numeric pain scores will be compared using t-test.
d) The total MME consumption will be calculated in the PGx and usual care groups on POD 0-7 and POD 1-14 using t-test.
e) The proportion patients experiencing an opioid related ADRs will be compared using a Fisher's exact test.
f) Proportion patients experiencing a NSAID-related ADRs in CYP2C9 variant carriers will be compared using a Fisher's exact test.
g) Baseline provider attitudes toward and knowledge of PGx testing using questions with Likert scales will be reported as means (SD). We will compare results by using linear regression.
h) Patient attitudes knowledge and satisfaction of PGx testing after completing the study using questions with Likert scales will be reported as means (SD). We will compare the results by using linear regression.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the PGx test, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to distributing to participant and collecting the PGx test buccal sample. The informed consent signature will be collected electronically through PennChart (Epic) or using a paper copy. A copy of the informed consent document will be given to the participants for their records either electronically via MPM or a paper copy if they do not have MPM. The following consent materials are submitted with this protocol: informed consent form.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The treating surgeon will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The informed consent will be collected in-person using a paper copy, electronically through PennChart (Epic), or verbally over the phone if the participant does not have MPM. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the PI if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, treating surgeons, and regulatory authorities. If the study is prematurely terminated

or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10.1.3 Confidentiality and Privacy

lnformation about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization.

All data related to this trial will be recorded using the patients' assigned unique study number. Data will be reported only in a confidential manner such that the personal identity of any subject will not be identifiable. All study data will be maintained under a double locked system, such as a locked closet within a locked office or on a password protected computer in a locked office. At the end of the study these data will be electronically archived on a password protected computer or other electronic storage device.

10.1.4 Future Use of Stored Specimens and Data

Samples are not stored for future use.

10.1.5 Source documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.1.6 Case report forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.1.7 Study monitoring, auditing, and inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.1.8 Safety Oversight

The Principal Investigator and Co-Investigators will be ultimately responsible for assuring the security of all study related materials to minimize risk to participants. Safety data such AEs and SAE will be assessed and reviewed in the PGx arm every 3 months after enrollment begins.

This study is expected to be classified as low risk by IRB. The intervention (PGx test) requires a self-collected buccal swab sample and thus poses limited risk compared to that experienced in daily life.

10.1.9 *Clinical Monitoring*

There is no external sponsor for this study. The PI will not complete the Principal Investigator's Compliance Assessment (PICA) form because this is a minimal risk research study.

10.1.10 Study Records Retention

Study documents and records will be retained for at least 2 years after the last participant has completed the study.

10.1.11 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

Not following the genotype guided dose recommendation is NOT considered a protocol deviation but will be recorded as one of the study outcomes.

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

10.1.12 Publication and Data Sharing Policy

This study will comply with the data sharing agreement.

10.1.13 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Protocol Amendment History

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the principal investigator. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. The principal investigator will submit protocol amendments to the appropriate regulatory authorities.

If in the judgment of, the sponsor, the IRB/IEC, and/or the investigator, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
2.0	11/21/22	Addition of contacting patients via phone for remote verbal or electronic consent. Also change of pharmacist “e-consult” to “consult”.	We are missing eligible patients if/when their surgery is not confirmed during the surgical consultation visit. The pharmacist will enter a consult note in the chart instead of the e-consult workflow.
3.0 - Was reviewed by Office of Regulatory Affairs and returned by IRB	1/17/23	Addition of Penn Health for Women Radnor as a recruitment site, Survey Code letter (13.8), and PRECISE Recruitment flyer (13.13),	We are adding Radnor as a recruitment site and created a recruitment flyer to help increase recruitment. The Survey code letter is to be mailed to the participant along with the pharmacist detailed note to patient summarizing results (13.7)

Version	Date	Description of Change	Brief Rationale
3.0	2/2/23	Addition of Penn Health for Women Radnor as a recruitment site and Survey Code letter (13.8)	We are adding Radnor as a recruitment site. The Survey code letter (13.8) was created to be mailed to the participant along with the already IRB-approved pharmacist detailed patient note that summarizes their results (13.7)
4.0	4/24/23	Addition of sites, clarification of inclusion criteria, when the detailed letters will be sent to participant's PCP, clarification of who is identifying participants, clarification that the survey sent to providers is optional, clarification that some baseline data will only be collected if available in the EHR, and updates to secondary endpoints to remove "in variant carriers".	Additional sites are being added to increase recruitment. Other changes are warranted to further clarify inclusion criteria, that certain data will only be collected if available, and who is identifying eligible participants.
5.0	8/29/23	Removal of PICA requirement. To ensure participants receive their PGx results, the PGx results will be released to the EHR and patient after 9 months from enrollment if the participant has not scheduled surgery.	This is a minimal risk research study and PICA is not required. Releasing results at 9 months will ensure that all participants will receive their PGx results.

11 STUDY FINANCES

11.1 Funding source

This study is financed through a grant from the Penn Center for Precision Medicine. All PGx testing fees will be covered by this study.

12 REFERENCES

1. Crews, K. R. *et al.* Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. *Clin. Pharmacol. Ther.* **110**, 888–896.

2. Theken, K. N. *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and Nonsteroidal Anti-inflammatory Drugs. *Clin. Pharmacol. Ther.* **108**, 191–200 (2020).
3. Smith, D. M. *et al.* CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **21**, 1842–1850 (2019).
4. Thomas, C. D. *et al.* A hybrid implementation-effectiveness randomized trial of CYP2D6-guided postoperative pain management. *Genet. Med.* **23**, 621–628 (2021).
5. Fingar, K. R., Stocks, C., Weiss, A. J. & Steiner, C. A. Most Frequent Operating Room Procedures Performed in U.S. Hospitals, 2003–2012: Statistical Brief #18. (2006).
6. Gan, T. J. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J. Pain Res.* **10**, 2287–2298 (2017).
7. ACOG Committee Opinion No. 750: Perioperative Pathways: Enhanced Recovery After Surgery. *Obstet. Gynecol.* **132**, e120–e130 (2018).
8. Obeng, A. O., Hamadeh, I. & Smith, M. Review of Opioid Pharmacogenetics and Considerations for Pain Management. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **37**, 1105–1121 (2017).
9. Grosser, T., Theken, K. N. & FitzGerald, G. A. Cyclooxygenase Inhibition: Pain, Inflammation, and the Cardiovascular System. *Clin. Pharmacol. Ther.* **102**, 611–622 (2017).
10. ibuprofen [package insert]. New York, NY: Pharmacia & Upjohn Company; 2007.
11. Klomp, S. D., Manson, M. L., Guchelaar, H.-J. & Swen, J. J. Phenoconversion of Cytochrome P450 Metabolism: A Systematic Review. *J. Clin. Med.* **9**, (2020).

12. Dunnenberger, H. M. *et al.* Preemptive Clinical Pharmacogenetics Implementation: Current programs in five United States medical centers. *Annu. Rev. Pharmacol. Toxicol.* **55**, 89–106 (2015).

13. Zhu, Y. *et al.* A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: preemptive, reactive, or none? *Genet. Med.* 1–10 (2020) doi:10.1038/s41436-020-00995-w.

14. Chanfreau-Coffinier, C. *et al.* Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users. *JAMA Netw. Open* **2**, e195345 (2019).

15. Hicks, J. K. *et al.* Implementation of Clinical Pharmacogenomics within a Large Health System: From Electronic Health Record Decision Support to Consultation Services. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **36**, 940–948 (2016).

16. Herr, T. M. *et al.* Pharmacogenomic clinical decision support design and multi-site process outcomes analysis in the eMERGE Network. *J. Am. Med. Inform. Assoc. JAMIA* **26**, 143–148 (2018).

17. Yeh, M.-L., Chang, Y.-J., Wang, P.-Y., Li, Y.-C. (Jack) & Hsu, C.-Y. Physicians' responses to computerized drug–drug interaction alerts for outpatients. *Comput. Methods Programs Biomed.* **111**, 17–25 (2013).

18. Bright, D. *et al.* Pharmacist Consult Reports to Support Pharmacogenomics Report Interpretation. *Pharmacogenomics Pers. Med.* **13**, 719–724 (2020).

19. Dean, L. Irinotecan Therapy and UGT1A1 Genotype. 12.

20. Wolkoff, A. W., Wolpert, E., Pascasio, F. N. & Arias, I. M. Rotor's syndrome. *Am. J. Med.* **60**, 173–179 (1976).

21. Cicali, E. J. *et al.* How to Integrate CYP2D6 Phenoconversion Into Clinical Pharmacogenetics: A Tutorial. *Clin. Pharmacol. Ther.* **110**, 677–687 (2021).

22. McPherson, M. L. *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, 2nd Edition*. (American Society of Health-System Pharmacists, 2018).

23. Busse, J. W. *et al.* Guideline for opioid therapy and chronic noncancer pain. *CMAJ Can. Med. Assoc. J.* **189**, E659–E666 (2017).

24. Grond, S. *et al.* High-Dose Tramadol in Comparison to Low-Dose Morphine for Cancer Pain Relief. *J. Pain Symptom Manage.* **18**, 174–179 (1999).

25. Wilder-Smith, C. H., Schimke, J., Osterwalder, B. & Senn, H.-J. Oral tramadol, a μ-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann. Oncol.* **5**, 141–146 (1994).

26. naproxen [package insert]. Basildon, Essex: Atnahs Pharma; 2016.

27. tramadol [package insert]. Gurabo, Puerto Rico: Janssen Ortho, LLC; 2008.

28. oxycodone [package insert]. Stamford, CT: Purdue Pharma LP; 2018.

13 APPENDICES

13.1 Schedule of Activities (SoA)

Study Procedures	Enrollment / Baseline	POD 0	POD 1	POD 2	POD 3	POD 7	POD 14	POD 30
Informed consent	X							
Inclusion and exclusion criteria	X							
Buccal swab collection	X							
Demographic data[1]	X							

Study Procedures	Enrollment / Baseline	POD 0	POD 1	POD 2	POD 3	POD 7	POD 14	POD 30
Diagnosis prompting surgical consultation	X							
Prior medical history	X							
Vital signs[2]	X	X	X	X	X	X	X	
Routine physical exam[3]	X							
Randomization	X							
Pharmacogenetic test	X							
Concomitant medications[4]	X							
Clinical chemistry[5]	X							
Creatinine clearance[6]	X							
Self-reported numeric pain score[7]		X	X	X	X	X	X	
Number of doses of pain medication taken per day while hospitalized[8]		X	X	X	X	X	X	
Total number of doses of pain medication taken after discharge[9]						X	X	
Opioids administered while hospitalized[10]		X	X	X	X	X	X	
Naloxone administration during hospitalization[11]		X	X	X	X	X	X	
Adverse event assessment for analgesics (opioids & NSAIDS)[12]		X	X	X	X	X	X	
Patient Survey[13]								X

1. Age, race/ethnicity, gender
2. Heart rate, blood pressure (POD 0, 1, 2, 3, 7, and 14 only during hospitalization)
3. Height/weight
4. Including dose, unit, frequency, route of administration and indication
5. Creatinine, AST, ALT (within 30 days of scheduled gynecologic surgery if available)
6. Using Cockcroft-Gault formula
7. Using a 0-10 numeric pain scale (POD 1 and 2 only during hospitalization)
8. Including daily calculated MME (POD 1 and 2 only during hospitalization)
9. Outpatient prescriptions doses: After discharge to POD 3, POD 4-7, POD 8-14, including total calculated MME
10. Names, doses, units, calculated MME, and dates/times
11. Dose, unit, and date/time of administration
12. See section 13.6.3
13. See section 13.11

13.2 CYP2D6 Phenoconversion

CYP2D6 Phenoconversion[21]

Steps:

1. Obtain/calculate genotype-based CYP2D6 activity score

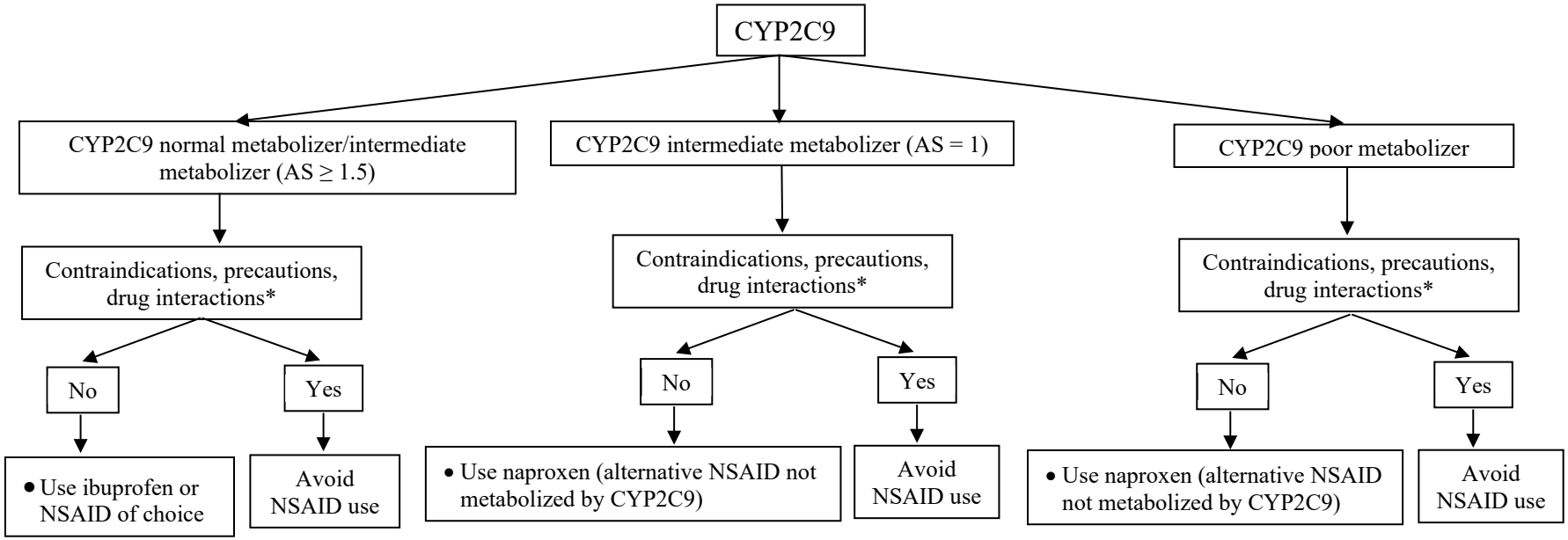
2. Assign phenotype 3. Multiple activity score by 0 (if taking a strong inhibitor) or 0.5 (if taking a moderate inhibitor) 4. Use adjusted CYP2D6 activity score to determine new CYP2D6 phenotype		
CYP2D6 inhibitor category	Medications	Multiply Genotype Activity Score by:
Strong inhibitors	Bupropion Fluoxetine Paroxetine Quinidine Terbinafine	0
Moderate inhibitors	Abiraterone Cinacalcet Duloxetine Lorcaserin Mirabegran	0.5

13.3 Morphine milligram equivalence

Opioids (in mg except where specified)	Equianalgesic conversions[22]
Codeine (oral): Morphine (oral)	6.7:1
Fentanyl (IV in mcg): Morphine (oral)	10:1
Hydrocodone (oral): Morphine (oral)	1:1
Hydromorphone (oral): Morphine (oral)	1:4
Hydromorphone (IV): Morphine (oral)	1:20
Morphine (IV): Morphine (oral)	1:3
Oxycodone (oral): Morphine (oral)	1:1.5
Tramadol (oral): Morphine (oral)*	10:1[23]

Mcg: micrograms
*Equianalgesic ratios of oral tramadol to oral morphine range from 4:1 to 10:1.[22–25] We have chosen to use a conservative conversion when converting tramadol to morphine equivalent doses.

13.4 Analgesic medication selection and dosing algorithm for CYP2C9

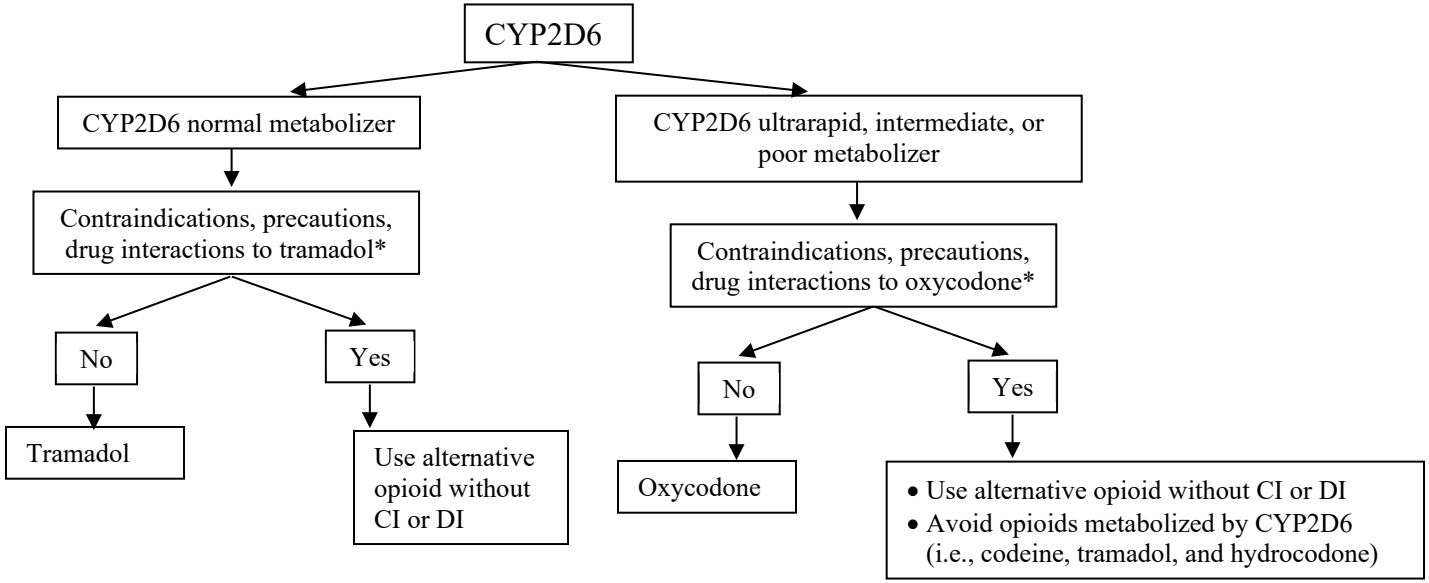


* Contraindications and precautions: Severe allergic reaction to any NSAIDs, recent CABG, active GI bleed/ulcer, cerebrovascular bleeding, severe hepatic impairment, severe renal impairment (CrCl < 30 mL/min), hyperkalemia, severe uncontrolled heart failure, third trimester of pregnancy
Major drug interactions: Acemetacin, anticoagulants (including DOACs), corticosteroids, cyclosporine, lithium, loop diuretics (specifically in patients with HF or cirrhosis), methotrexate, micamorelin, mifamurtide, NSAIDs, phenylbutazone, pralatrexate, salicylates, SSRIs/SNRIs, sincalide, sodium phosphates, tenofovir, urokinase

AS activity score; NSAID non-steroidal anti-inflammatory; CABG coronary artery bypass surgery; GI gastrointestinal; CrCl creatinine clearance; DOAC direct oral anticoagulants; HF heart failure; SSRI selective serotonin reuptake inhibitors; SNRI serotonin norepinephrine reuptake inhibitors

ibuprofen[10] naproxen[26]

13.5 Analgesic medication selection and dosing algorithm for CYP2D6[27]



* Contraindications and precautions: Severe allergic reaction to opioid (recommendations for opioids in non-cross-reactive opioid subclasses will be made if applicable), severe hypotension, GI obstruction, paralytic ileus; seizure disorder (avoid tramadol, use caution with other opioids); MAOI in last 14 days; acute pancreatitis; use caution combining tramadol and other drugs that may reduce seizure threshold (neuroleptics)
Major drug interactions ***(those italicized and bolded are specific to tramadol): SSRIs (C), SNRIs (C), TCAs, tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc)***, abametapir, alvimopan, azelastine, blonanserin, bromperidol, ***carbamazepine***, chlormethiazole, use caution with other CNS depressants (including other opioids), ***dapoxetine***, droperidol, eluxadoline, fexinidazole, flunitrazepam, fusidic acid, ***iobenguane, iohexol, iomeprol, iopamidol***, kratom, lemborexant, ***linezolid, methylene blue***, MAOIs, methotimeprazine, nefazodone, nalmefene, naltrexone, orphenadrine, oxomemazine, ***oxybate salt products***, paraldehyde; phenobarbital, primidone, ropeginterferon alfa-2b, samidorphan, sincalide, suvorexant, zolpidem

Chemical classes or opioids (cross sensitivity): Phenanthrenes: buprenorphine, butorphanol, codeine, dextromethorphan, hydrocodone, hydromorphone, levorphanol, methylnaltrexone, morphine, nalbuphine, naloxone, naltrexone, oxycodone, oxymorphone; Phenylpiperadines: alfentanil, fentanyl, meperidine, remifentanil, sufentanil; Diphenylheptanes: methadone, propoxyphene; Phenylpropyl amines: tramadol
CI contraindication; DI drug interaction; GI gastrointestinal; MAOI monoamine oxidase inhibitor

oxycodone[28] tramadol[27]

13.6 Medication information

13.6.1 Dosing information for oral analgesics

Medication class	Medication	Initial dose	Range	Max/24 hours
Opioids	Oxycodone (IR)[28]	5 mg PO Q4-6H prn	5-10 mg PO Q4-6H	
	Tramadol (IR)[27]	50 mg PO Q4-6H prn	25-100 mg PO Q4-6H	400 mg
NSAIDs (Short-acting)	Ibuprofen[10]	200-400 mg PO Q4-6H prn or scheduled	200-800 mg PO Q4-6H	3200 mg
	Naproxen[26]	500 mg once, followed by (250-500mg PO Q12 or 250 mg PO Q6-8H) prn or scheduled	250-500 mg PO Q6-12H	1250 mg on day 1, then 1000 mg thereafter
IR = immediate release; H = hours; Q = every				

13.6.2 Dosing adjustments for clinical factors

Medication	CrCl 30-60 mL/min	CrCl< 30 mL/min	Hemodialysis	Hepatic impairment	Elderly > 75 years
Oxycodone	50-75% of usual dose, no more frequent than Q6H	50% of usual dose, no more frequent than Q8H	50% of usual dose no more than Q8H	33-50% of usual dose	
Tramadol		Increase dosing interval to Q12H (max: 200 mg/day)	25 mg twice daily (max 100-200 mg/day)	Severe*: 50 mg Q12H	Max: 300 mg/day
Ibuprofen	Use lowest effective dose	</= 30 mL/min avoid use			
Naproxen	Use lowest effective dose	</= 30 mL/min avoid use			
*Child-Pugh class C CrCl creatinine clearance; Q = every; H = hours					

13.6.3 Clinical adverse drug reaction profile

Most common adverse drug reactions for opioids							
ADR	**Codeine**	**Fentanyl**	**Hydrocodone**	**Hydromorphone**	**Morphine**	**Oxycodone**	**Tramadol**
Abdominal pain	X			X		X	X
Adrenal insufficiency	X	X	X	X		X	
Apnea		X		X	X		
Bradycardia		X			X		
Cardiovascular depression (severe)	X	X	X	X	X	X	
Constipation	X		X	X	X	X	X
Diarrhea				X			X
Dizziness	X	X	X	X	X	X	X
Dry mouth				X		X	X
Dysphoria	X		X	X	X		
Euphoria	X			X	X		X
Flushing				X	X		
Headache					X	X	X
Hypertension		X		X			
Hypotension	X	X	X	X	X	X	
Laryngospasm		X		X		X	
Light-headedness	X		X	X	X		
Nausea	X	X	X	X	X	X	X
Pruritis	X	X	X	X	X	X	X
Rash	X	X	X	X	X	X	X
Respiratory depression	X	X	X	X	X	X	
Rigidity		X					
Sedation	X	X	X	X	X		
Seizures*	X	X	X	X		X	X†
SOB	X						
Skeletal muscle rigidity		X		X			
Sweating	X	X		X	X	X	X
Vomiting	X	X	X	X	X	X	X

Color Key:	Serious ADRs: Included in boxed warning or warning/precaution section of PI	Most common ADRs

*Increased risk in patients with seizure disorders

† Seizure risk is increased with concomitant use of SSRIs, TCAs, tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc), other opioids, MAO inhibitors, neuroleptics, or other drugs that reduce seizure threshold

SOB shortness of breath; ADR adverse drug reaction

Most common adverse drug reactions for non-steroidal anti-inflammatory drugs (NSAIDs)							
ADR	**Celecoxib**	**Flurbiprofen**	**Ibuprofen**	**Ketorolac**	**Meloxicam**	**Naproxen**	**Piroxicam**
Abdominal pain	X	X	X	X	X	X	X
Appetite (↓)			X				
Bleeding (↑risk)		X	X	X	X	X	X
↑ Bleeding time		X	X	X	X	X	X
Constipation		X	X	X			X
CTE	X	X	X	X	X	X	X
Diarrhea	X	X	X	X	X		X
Dizziness	X		X	X	X	X	X
Dyspepsia	X	X		X	X	X	X
Ecchymosis						X	
Edema	X	X	X	X	X	X	X
Epigastric pain			X				
Flatulence	X	X	X	X	X	X	X
GI bleed/ulcer	X	X	X	X	X	X	X
Headache		X	X	X	X	X	X
Heartburn			X	X		X	X
Hemoglobin (↓)	X	X	X	X	X	X	X
Hyperkalemia		X	X	X	X	X	X
Hypertension	X	X	X	X	X	X	X
Indigestion			X				
Influenza-like Sx					X		
Liver enzymes (↑)	X	X	X	X	X	X	X
Nausea		X	X	X	X	X	X
Pharyngitis	X				X		
Rash	X		X	X	X	X	X
Renal dysfunction	X	X	X	X	X	X	X
Rhinitis	X						
Sinusitis	X						
Tinnitus	X			X		X	X
URI	X				X		
Vomiting		X	X	X	X	X	
Color Key:	Serious ADRs: Included in boxed warning or warning/precaution section of PI				Most common ADR for all NSAIDs		

ADR adverse drug reaction; CTE cardiovascular thrombotic events (including myocardial infarction and stroke); PI package insert; Sx symptoms; URI upper respiratory tract infection

13.7 Pharmacist detailed note to patient summarizing PGx results

Introduction: Pharmacogenetic (PGx) Testing

Pharmacogenetic (PGx) tests are **genetic tests** that help predict how you will respond to some medications and the results help your medical team make decisions about which medications may work best for you. People have differences in these genes and this test helps to explain why people respond differently to the same medication. Differences in these genes can 1) increase the person's risk of side effects to some medications or 2) decrease how well the medication will work for them.

Key terms to consider when reviewing your PGx results:

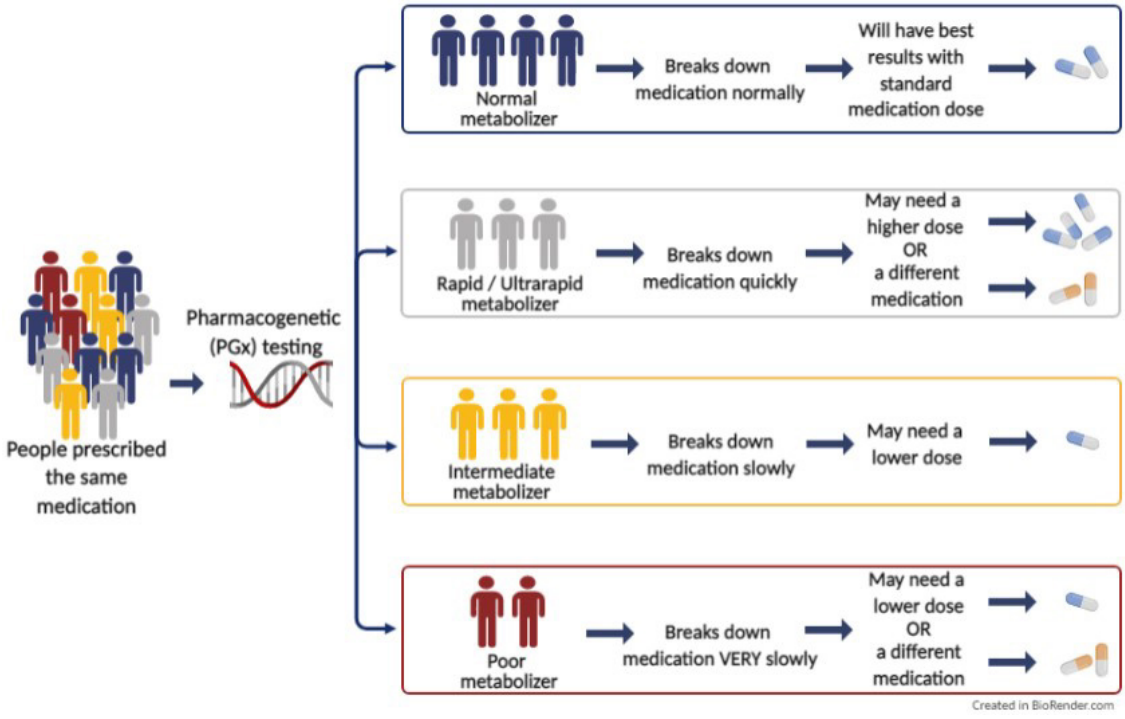
Gene: Each gene is a separate instruction guide for a protein that is needed for medications to work in the body. An example of a gene is *CYP2C19.*

Allele: We all have two copies of each gene, one from each parent. A single gene copy is referred to as an allele, you have one allele from your mother and one from your father. The alleles are coded by a naming system using numbers and stars (*). An example of an allele for the *CYP2C19* gene is *2.

Genotype: Together a pair of alleles is called a genotype. Each gene allele may give the same or slightly different instructions. The genotype tells which two alleles you carry for each gene. An example genotype for the *CYP2C19* gene is *1/*2.

Phenotype: The phenotype predicts how well the proteins created from your two alleles for each gene will work. Each person can have a different phenotype for each gene. For the above example gene and genotype, *CYP2C19* *1/*2, the phenotype would be intermediate metabolizer.

The below figure is an example of how variations in these genes can impact how a person will respond to a medication.



The first part of the report includes detailed information about each gene that was tested. The second part has recommendations from the pharmacist to help you and your healthcare providers make choices about medications. These recommendations may change in the future as new drugs are developed and as we learn more about gene-drug interactions.

Part I: Gene results

This section lists the actionable genes that were tested, which alleles are present in your body (genotype), and how your alleles are expected to affect drug metabolism and drug response (phenotype).

Actionable Pharmacogenetic Results:

Gene	Genotype	Phenotype
CYP2B6		
CYP2C19		
CYP2C9		
CYP2C Cluster		
CYP2D6		
CYP3A5		
CYP4F2		
DPYD		
IFNL4		
HLA-A		
HLA-B		
NUDT15		
SLCO1B1		
TPMT		
UGT1A1		
VKORC1		

Normal Pharmacogenetic Results

Gene	Genotype	Phenotype
CYP2B6		
CYP2C19		
CYP2C9		
CYP2C Cluster		
CYP2D6		
CYP3A5		
CYP4F2		
DPYD		
IFNL4		
HLA-A		

HLA-B		
NUDT15		
SLCO1B1		
TPMT		
UGT1A1		
VKORC1		

Part II: Medication recommendations

This section provides specific medication recommendations based upon your pharmacogenetic results. The recommendations reflect clinical practice guidelines at the time of this report. Discuss these results with your medical team, including a pharmacist, prior to starting new medications or making changes to your current medications.

Use These Medications with Great Caution or Consider Alternatives

- May have serious side effects
- May have little to no drug response
- May need a higher or lower dose of drug

***				
Drug Name	**Gene(s)**	**Common uses**	**Clinical impact**	**Recommendation (Intended for healthcare providers only)**

These Medications May Require Dose Adjustment Along With More Frequent Monitoring

- May have some side effects
- May have less than optimal drug response
- May need a higher or lower dose of drug

***				
Drug Name	**Gene(s)**	**Common uses**	**Clinical impact**	**Recommendation (Intended for healthcare providers only)**

The above report summarizes your actionable genetic results. Actionable means there is enough scientific evidence to make clinical decisions using these gene tests. The results will be placed into your electronic health record to assist your medical care team at Penn Medicine in prescribing decisions.

The information in this report is for general educational purposes and is not intended to be a substitute for professional medical advice. Only a physician, pharmacist, or other healthcare provider should advise you on your prescribed medications.

The lab only reports select variants but not all variants in the genes. It is possible that you may have variants that were not tested. The results of the genetic testing will not change, but the scientific knowledge surrounding the impact of these genes on drug response is always changing, so that in the future we will have more knowledge on how these may predict side effects or efficacy of medications. Visit https://cpicpgx.org/genes-drugs/ for up-to-date evidence.

Many side effects of medications cannot be explained by currently known genetics factors. These genetic results are only one of the clinical components that your provider uses when selecting a medication and dose for you. Other factors such as drug interactions, lab results, age, sex, past medical history, weight, height, etc. are also important considerations.

We recommend that you present this report to every doctor, physician assistant, nurse practitioner, and clinician you see, as well as your pharmacist. The pharmacogenetics pharmacist at Penn Medicine is available during regular business hours for questions regarding these test results. You may contact the pharmacogenetics pharmacist or a genetic counselor through the Medical Genetics Clinic at (215) 662-4740.

Report completed by/Date:

_____/_____

13.8 Survey Code Letter

Hello ***,
Thank you for participating in our research study called **P**ha**R**macog**E**netic-guided **C**ho**I**ce of post-**S**urg**E**ry analgesics (PRECISE). In this envelope you will find a detailed letter explaining your pharmacogenetic results.
Additionally, an email was sent to *** on *** with directions for how to activate your Greenphire ClinCard (reloadable, prepaid card). A total of $*** has been added to this card for completing *** out of 3 text messages surveys after your surgery.

We previously texted you a link to a survey on *** that you haven't completed yet. If you complete this brief survey shown below, an additional $15.00 will be added to your card.

Survey title: "**Experience and satisfaction with pharmacogenetic testing**"

Please follow the instructions below to navigate to the survey page. To start the survey, you may use either of the two choices (the Survey Access Code or the QR code), whichever you find easiest or quickest to use.

Enter the Survey Access Code

Start the survey by following the steps below.

1.) Go to this web address:

https://redcap.med.upenn.edu/surveys/

2.) Then enter this code:

***

Scan the QR Code

Alternatively, if you have a device that has an app capable of reading QR codes, you may scan the QR code below, which should take you directly to the survey in a web browser.

Thank you,
The PRECISE Research Study Team
Contact: precise@pennmedicine.upenn.edu

13.9 Pharmacist PGx-guided recommendations to providers consult note template

Pharmacist Pharmacogenetic (PGx) Consultation

*** is a ***-year-old *** who is scheduled to have *** on ***. He/She underwent pharmacogenetic testing using the OneOme RightMed® test panel, ordered by *** on ***.

Reason for consultation: Pharmacogenetic-guided postoperative pain medication recommendations.

Medical history pertaining to this genetic result and pain medication recommendation (obtained from the EHR)
***

Current medications
***

Drug allergies/intolerances
***

Pertinent lab results
***

Pharmacogenetic results:
Dr. ***, PharmD, a pharmacist with specialized training in pharmacogenomics reviewed the pharmacogenetic results. Only actionable pharmacogenomic results are listed in this note. To see an exclusive list of all pharmacogenes tested, refer to the OneOme lab report, easily found in the genomics tab of the EHR.

- Gene genotype phenotype

- Gene genotype phenotype

Assessment/Plan: The below recommendations are for those drug-gene interactions (DGIs) where there is enough scientific evidence to support clinical decisions.

General pharmacogenomic testing information. The lab only reports select variants but not all variants in the genes. It is possible that the patient may have variants that were not tested. The results of the genetic testing will not change, but the scientific knowledge surrounding the impact of these genes on drug response is always changing, so that in the future we will have more knowledge on how these may predict side effects or efficacy of medications. Many side effects of medications cannot be explained by currently known genetics factors. Visit https://cpicpgx.org/genes-drugs/ for up-to-date evidence.

- **Postoperative pain.**
- **Postoperative nausea/vomiting.**

13.10 Text messaging script

Pha**R**macog**E**netic-guided **C**ho**I**ce of post-**S**urg**E**ry analgesics (**PRECISE**)
Text messaging script via RedCap for the survey and Twilio for SMS service on postop days 3, 7, & 14

Post-op Day 3 Text Message Script	
"Hello this is the PRECISE study team at Penn Medicine! You enrolled in this study prior to your gynecologic surgery. The goal of the PRECISE study is to understand if pharmacogenetic tests are useful to guide the choice of pain medication following surgery. We have a few questions for you. Text 'YES' if we can ask you a few questions about how you are managing your pain. Text 'STOP' anytime to opt-out. Texting is not secure. Other people may be able to see information in text messages. By texting back 'YES' you are accepting this risk. Message & data rates may apply."	
Question 1:	How would you rate your pain over the past 24 hours? (From 0-10, 0 being no pain [please choose one number])
Question 2:	Have you taken [narcotic_RX] for your pain after you were discharged from the hospital (at home)? [Y for yes or N for no]."
	LOGIC: ➢ If yes, proceed to question 3 ➢ If no, proceed to question 5
Question 3:	"Please estimate how many pills of [narcotic_RX] you have taken after you were discharged from the hospital (at home)? Please text back a number."
Question 4:	*"How many pills of [narcotic_RX] are remaining in your bottle? Please text back a number."*
Question 5:	"Have you taken any of the following medications for your pain after you were discharged from the hospital (at home): acetaminophen (TYLENOL), ibuprofen (ADVIL/MOTRIN), or naproxen (ALEVE/NAPROSYN)? [enter 1 for acetaminophen (TYLENOL), 2 for ibuprofen (ADVIL/MOTRIN), 3 for naproxen (ALEVE/NAPROSYN), or 4 if you have taken a combination of these meds]."

Question 6:	"Do you plan to continue taking medication to control your pain? [enter 1 for acetaminophen (TYLENOL), 2 for ibuprofen (ADVIL/MOTRIN), 3 for naproxen (ALEVE/NAPROSYN), 4 {narcotic_RX}, or 5 if you plan to take a combination of these meds]."
Final statement	"Thanks! When you're finished, it's important to dispose of unused %narcotic%. You can do so at any Penn Pharmacy"

Post-op Day 7 Text Message Script	
"Hello this is the PRECISE study team at Penn Medicine! You enrolled in this study prior to your gynecologic surgery. The goal of the PRECISE study is to understand if pharmacogenetic tests are useful to guide the choice of pain medication following surgery. We have a few questions for you. Text 'YES' if we can ask you a few questions about how you are managing your pain. Text 'STOP' anytime to opt-out. Texting is not secure. Other people may be able to see information in text messages. By texting back 'YES' you are accepting this risk. Message & data rates may apply."	
Question 1:	How would you rate your pain over the past 24 hours? (from 0-10, 0 being no pain [please choose one number])
Question 2:	Have you taken [narcotic_RX] for your pain in the last 4 days? [Y for yes or N for no]."
	LOGIC: ➢ If yes, proceed to question 3 ➢ If no, proceed to question 5
Question 3:	"Please estimate how many pills of [narcotic_RX] you have taken in the last 4 days? Please text back a number."
Question 4:	*"How many pills of [narcotic_RX] are remaining in your bottle? Please text back a number."*
Question 5:	"Have you taken any of the following medications for your pain in the last 4 days: acetaminophen (TYLENOL), ibuprofen (ADVIL/MOTRIN), or naproxen (ALEVE/NAPROSYN)? [enter 1 for acetaminophen (TYLENOL), 2 for ibuprofen (ADVIL/MOTRIN), 3 for naproxen (ALEVE/NAPROSYN), or 4 if you have taken a combination of these meds]."
Question 6:	"Do you plan to continue taking medication to control your pain? [enter 1 for acetaminophen (TYLENOL), 2 for ibuprofen (ADVIL/MOTRIN), 3 for naproxen (ALEVE/NAPROSYN), 4 {narcotic_RX}, or 5 if you plan to take a combination of these meds]."
Final statement	"Thanks! When you're finished, it's important to dispose of unused %narcotic%. You can do so at any Penn Pharmacy"

Post-op Day 14 Text Message Script
"Hello this is the PRECISE study team at Penn Medicine! You enrolled in this study prior to your gynecologic surgery. The goal of the PRECISE study is to understand if pharmacogenetic

tests are useful to guide the choice of pain medication following surgery. We have a few questions for you. Text 'YES' if we can ask you a few questions about how you are managing your pain. Text 'STOP' anytime to opt-out. Texting is not secure. Other people may be able to see information in text messages. By texting back 'YES' you are accepting this risk. Message & data rates may apply."	
Question 1:	How would you rate your pain over the past 24 hours? (from 0-10, 0 being no pain [please choose one number])
Question 2:	Have you taken [narcotic_RX] for your pain over the past 7 days? [Y for yes or N for no]."
	LOGIC: ➢ If yes, proceed to question 3 ➢ If no, proceed to question 5
Question 3:	"Please estimate how many pills of [narcotic_RX] you have taken in the past 7 days? Please text back a number."
Question 4:	*"How many pills of [narcotic_RX] are remaining in your bottle? Please text back a number."*
Question 5:	"Have you taken any of the following medications for your pain in the last 7 days: acetaminophen (TYLENOL), ibuprofen (ADVIL/MOTRIN), or naproxen (ALEVE/NAPROSYN)? [enter 1 for acetaminophen (TYLENOL), 2 for ibuprofen (ADVIL/MOTRIN), 3 for naproxen (ALEVE/NAPROSYN), or 4 if you have taken a combination of these meds]."
Question 6:	"Do you plan to continue taking medication to control your pain? [enter 1 for acetaminophen (TYLENOL), 2 for ibuprofen (ADVIL/MOTRIN), 3 for naproxen (ALEVE/NAPROSYN), 4 {narcotic_RX}, or 5 if you plan to take a combination of these meds]."
Question 7:	*"Thank you so much! Just one more question for you. How many days did it take for your pain to improve after your procedure/surgery?"* [please enter a number]
Final statement	"Thanks! When you're finished, it's important to dispose of unused %narcotic%. You can do so at any Penn Pharmacy"

13.11 Provider survey – Pharmacogenetic testing

Provider Pharmacogenomics (PGx) Questionnaire

The intent of this questionnaire is to identify attitudes, interest, and knowledge of healthcare professionals regarding pharmacogenetic testing (PGx).

This questionnaire should take you less than 10 minutes to complete. Thank you for your support.

1. **Number of years in practice.**
   - ○ 0 – 5 years
   - ○ 6 – 10 years
   - ○ 11 – 15 years
   - ○ 16 – 20 years

- ○ 21+ years

2. **What is your profession?**
   - ○ Physician
   - ○ Non-physician provider
   - ○ Other

3. **What is your specialty/area of practice?**
   - ○ General gynecologic surgery
   - ○ Gynecologic Oncology surgery
   - ○ Other (please specify):

4. **State your gender.**
   - ○ Male
   - ○ Female
   - ○ Non-binary
   - ○ Prefer not to say
   - ○ Prefer to self-describe

5. **I have heard of pharmacogenetics or pharmacogenomics (PGx) before.**
   - ○ Yes
   - ○ No

6. **How often do you order PGx tests to assist with medication selection or dosing?**
   - ○ Never
   - ○ 1-5 times a year
   - ○ 6-10 times a year
   - ○ 11-25 times a year
   - ○ More than 25 times a year
   - ○ Not sure

7. **At some point in my practice, a patient has come to me with PGx test results.**
   - ○ Yes
   - ○ No

8. **I believe gene-drug interactions (i.e., when a patient's PGx results affect the metabolism of a drug) are as clinically important as drug-drug interactions.**
   - ○ Strongly agree
   - ○ Agree
   - ○ Neutral
   - ○ Disagree
   - ○ Strongly disagree

9. **I believe PGx testing can improve care for patients.**
   - ○ Strongly agree
   - ○ Agree
   - ○ Neutral
   - ○ Disagree
   - ○ Strongly disagree

10. I am confident in my ability to use the results of PGx testing in prescribing medications.

- ○ Strongly agree
- ○ Agree
- ○ Neutral
- ○ Disagree
- ○ Strongly disagree

11. PGx variations can impact the efficacy and/or safety of a medication. Which of the following scenarios are you likely to order a PGx test <u>before</u> prescribing a medication (select all that apply):

- ☐ If the PGx test can predict efficacy of the drug
- ☐ If the PGx test can predict risk of side effects to the drug
- ☐ If the PGx test can help to achieve the target therapeutic dose more quickly
- ☐ If the Food & Drug Administration (FDA) labeling recommends PGx testing

12. I am aware that FDA product labeling can contain PGx information, that helps clinicians apply PGx results in clinical practice.

- ○ I was aware of this
- ○ I was **<u>not</u>** aware of this

13. If I had PGx test results for a patient, it would be helpful to consult with a pharmacist for their interpretation and recommendations on medication selection and dosing.

- ○ Strongly agree
- ○ Agree
- ○ Neutral
- ○ Disagree
- ○ Strongly disagree

14. The following barrier(s) prevent me from using PGx in practice. (Select all that apply)

- ☐ Access to a laboratory that can perform a PGx test
- ☐ Access to clinical PGx specialists
- ☐ Cost of the test or insurance coverage
- ☐ Ethical concerns
- ☐ Lack of inclusion of PGx data in society guidelines
- ☐ Little training or experience with PGx
- ☐ Turnaround time for the test results (estimate 1-2 weeks)
- ☐ Other (please specify)

15. In your opinion, what are effective methods to educate clinicians about PGx testing? (Select all that apply)

- ☐ Case conference
- ☐ Conference or symposium (half or full day)
- ☐ Grand rounds or other types of in-house seminars
- ☐ Online module
- ☐ PGx training in school
- ☐ PGx training in residency
- ☐ Publication in scientific journals that I read regularly
- ☐ Webinar

- ☐ Other (Please specify)
- ☐ PGx education is not necessary

16. Please provide any additional comments or thoughts about PGx testing in the box below.

13.12 Patient survey – Pharmacogenetic testing

EXPERIENCE AND SATISFACTION WITH PHARMACOGENETIC TESTING IN GYNECOLOGIC SURGERY PATIENTS

PLEASE COMPLETE THE SURVEY BELOW. THE SURVEY SHOULD TAKE ABOUT 15 MINUTES TO COMPLETE.

THANK YOU!

1. First name:	
2. Last name:	
3. Please enter your age:	
4. What is the highest degree or level of school you have completed?	○ Less than high school ○ High school graduate (or GED) ○ Some college/university ○ College/university graduate ○ Post college/university degree ○ Choose not to respond
5. How confident are you in filling out forms in a doctor's office by yourself?	○ Extremely ○ Somewhat ○ A little bit ○ Not at all
6. Have you ever had a bad reaction from a medication that led to stopping the medication or going to the hospital?	○ Yes ○ No ○ I am unsure
7. How many different prescriptions do you take regularly?	○ 0 ○ 1-2 ○ 3-5

- ○ 6-10
- ○ 11 or more

A pharmacogenetic (PGx) test is a type of genetic test that could allow doctors to choose the right medication that will work for a patient or avoid using certain medications that may cause sideeffects.

- You had pharmacogenetic (PGx) testing at the surgeon's office prior to your gynecologic surgery to help guide pain medication selection and dosing. You used a swab along the inside of your cheek to collect a saliva sample for this test.
- Please answer the following questions based on your experience and satisfaction with pharmacogenetic testing:

	Strongly Agree	Agree	Unsure	Disagree	Strongly Disagree
8. I understand the purpose of pharmacogenetic (PGx) testing.	i	i	i	i	i
9. The cheek swab for the PGx test was easy to perform.	i	i	i	i	i
10. My physician explained my PGx test results to me.	i	i	i	i	i
11. I understand the PGx test results that I received.	i	i	i	i	i
12. I am confused about my PGx test results.	i	i	i	i	i
13. Based on my PGx test results, I learned something new about the medications I am or was taking.	i	i	i	i	i
14. After having PGx testing, I am more confident that the pain medication I was prescribed worked better for me.	i	i	i	i	i
15. I think the PGx test results were helpful to my doctor when they decided what pain medication to give me.	i	i	i	i	i
16. I am satisfied with the PGx test.	i	i	i	i	i

17. I would recommend PGx testing to a family member or friend.	i	i	i	i	i
18. I would like to talk to a PGx specialist to further explain my results.	i	i	i	i	i
19. I am happy that I now know my PGx test results to help guide future medication choices.	i	i	i	i	i
20. I plan on sharing my PGx test results with all my healthcare providers to help in deciding what medication and dose to prescribe me.	i	i	i	i	i

21. How did you learn about your PGx test results?

- ○ In-person by my physician
- ○ In my online chart (My Penn Medicine)
- ○ By another healthcare professional
- ○ I don't remember
- ○ I didn't learn about my PGx results