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TITLE: Evaluating the Use of Preemptive Pharmacogenomic Testing to Personalize Supportive Oncology

Short title: Pharmacogenomic Testing to Personalize Supportive Oncology

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American Cancer Society

The study will be conducted in compliance with the protocol, ICH/GCP, and any applicable regulatory requirements.

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PROTOCOL SIGNATURE PAGE
PROTOCOL TITLE: A Prospective Trial Evaluating the Use of Preemptive Pharmacogenomic Testing to Personalize Supportive Oncology

VERSION No.: v7.0
VERSION DATE: 02/20/2024

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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Signature of Sponsor-Investigator Date

Jai N. Patel

Sponsor-Investigator Name (printed)

SYNOPSIS

TITLE	**Evaluating the Use of Preemptive Pharmacogenomic Testing to Personalize Supportive Oncology**
STUDY POPULATION	Adult cancer patients ≥ 18 y/o presenting with moderate to high pain (≥ 4/10) and/or depression (≥3/10 or patients diagnosed with depression with a clinical need to adjust depression medications) on the Edmonton Symptom Assessment Scale (ESAS) during the initial consultation or a follow-up visit that occurs more than 1 year since the last visit in the palliative medicine clinic, able and willing to sign informed consent, and able to provide a buccal sample for pharmacogenetic testing.
SUMMARY OF STUDY RATIONALE	Over 90% of cancer patients experience cancer- or treatment-related symptoms, including pain and depression. At least 50% have uncontrolled symptoms throughout their lifetime. This significantly impacts patients' quality of life, response to therapy, and potentially survival. Many medications used to treat these symptoms are plagued with a system of trial and error, with prolonged time to symptom control or improvement. Objective tools are needed to improve drug selection and reduce symptom burden. Pharmacogenetics (PGx) allows for personalized medical decisions based on patient-specific genetics and provides a unique opportunity to reduce arbitrary drug selection and improve personalized prescribing, especially for pain and depression medications. By studying the application of a PGx test to alter drug prescribing patterns and improve treatment outcomes in supportive oncology, these results will provide critical information to understand the feasibility and utility of performing preemptive, real-time PGx testing. We believe this study will help shift supportive care prescribing paradigms from a trial-and-error approach to a personalized, genomics-driven method. Ultimately, using PGx to optimize medication selection and control cancer-related symptoms may improve quality of life throughout the cancer care continuum, potentially extending overall survival.
STUDY DESIGN	This is a prospective clinical trial of adult cancer patients presenting with pain and depression, newly referred to the Department of Supportive Oncology's palliative medicine clinic (or previously established patients without a visit in the past year) and receiving PGx testing for genes related to supportive care prior to their Baseline study visit. Patients will be screened and identified for eligibility after their initial consultation in palliative medicine. If meeting the ESAS score cutoffs for pain and depression and meeting all other eligibility criteria, patients will be approached for consent and undergo buccal swabs collection after informed consent is obtained. Genotyping results will be returned within approximately 4-5 business days. A PGx specialist will provide detailed clinical interpretations to the referring provider and upload a copy of the test results into the subject's medical chart. A consultation note will also be placed in each subject's chart detailing the pharmacogenomics results. Supportive Oncology clinicians will be instructed to consult a pharmacist to evaluate PGx test results prior to prescribing supportive care therapies, especially pain and depression medications. The number of consults and recommendations will be documented, in addition to test results, demographic data, medical/medication history, ESAS symptom scores, PHQ9 depression scores, and side effects of supportive therapy. The

	number of ambulatory clinic visits and hospitalizations will be used to estimate health care utilization and costs. Subjects will complete a short survey at the end of the study period regarding their knowledge about PGx, and whether access to PGx information improves satisfaction with care and communication.
OBJECTIVES	Primary Objective: • To estimate the proportions of subjects undergoing PGx testing who receive at least one drug/dose selection or modification based on their test results within any of the study visits where PGx results are available. • Secondary Objectives: • To determine the impact of PGx on treatment outcomes by measuring pain scores using the Edmonton Symptom Assessment Scale (ESAS) (Appendix A) and depression scores using the Patient Health Questionnaire (PHQ) 9 (Appendix B) at study visits after the Baseline study visit. Symptom scores will also be compared between those receiving PGx testing and a matched control receiving clinical management alone. • To describe subject perspectives (Appendix C) of PGx testing using a survey administered to subjects after/at the Final visit (or sooner if withdrawn). • Exploratory objectives: • To determine the types & frequencies of actionable genotypes that result in drug/dose selection or modification(s) and those that do not result in drug/dose selection or modification(s). • To describe the types of new medications prescribed (using medications of interest list; Appendix D) or medication/dose adjustments based on the PGx results. • To determine the type & frequency of drug/gene interactions present at the Baseline and the Final study visit using CPIC guidelines and FDA's pharmacogenomics table. • Summarize PGx best practice advisory alerts among participants enrolled after the transition to Epic to describe the proportion of participants that had a BPA fire in the EMR, the number and type of BPAs per participant, and any actions taken from the BPA.
KEY INCLUSION CRITERIA	• Adult cancer patients ≥ 18 years of age who have had either an initial visit in the Department of Supportive Oncology's palliative medicine clinic or a re-establishment of care visit with the last visit being at least 1 year prior, able and willing to sign the informed consent and provide a buccal sample for PGx testing. • Hematologic malignancy or any stage solid tumor malignancy. Presenting with pain score ≥ 4/10 and/or depression score ≥ 3/10 on ESAS (or patients diagnosed with depression with a clinical need to adjust depression medications)
STATISTICAL CONSIDERATIONS	The evaluable population for the primary objective is defined as enrolled subjects with confirmed malignancy (per provider documentation) completing an on-study visit with PGx results available. We anticipate enrolling 80 eligible subjects, of which we estimate 65 will be evaluable.

	With this sample size, the width of the 95% Clopper-Pearson confidence interval will be ≤25%, regardless of the observed DDSM rate.
NUMBER OF SUBJECTS	80, to achieve 65 evaluable subjects

SCHEMA

Cancer patients seen at the Department of Supportive Oncology's Palliative medicine clinic

↓

ESAS: patients with pain ≥ 4/10 and/or depression ≥3/10 (or diagnosed with depression and needs changes to depression medications per provider) will be screened for eligibility at initial consultation

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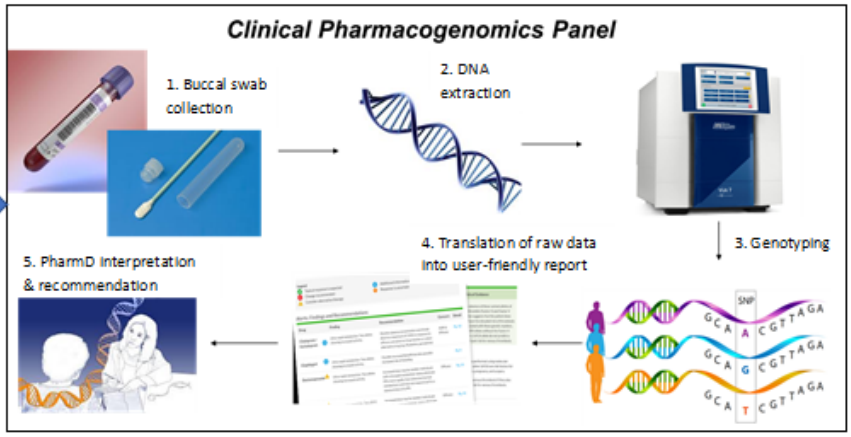
Meets ESAS criteria: potential subject contacted to determine interest and obtain on-site consent or schedule and obtain an eConsent

↓

After consent:

Subject will provide 2 buccal swabs for PGx testing

(mail-in or collect on site)



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PGx test report and consult note uploaded into subject EMR

*Buccal swab may occur as early as day of consent, but at least one week before baseline visit. **Turnaround time for PGx report is approximately 4 days.**

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Day 0

Baseline visit

→ Subject demographics, medical history, treatment history, drug allergies, medications, ESAS, PHQ9, HCRU, PGx use

↓

3 Study Visits every 4 weeks (± 1 week)

→ ESAS, PHQ9, change in medications, use of PGx to guide/modify pharmacotherapy regimen, HCRU, drug allergies. Medication interventions may also be made between clinic visits.

↓

Final Study Visit

4 weeks (± 1 week) after the third completed Study Visit

→ ESAS, PHQ9, change in medications, use of PGx to guide/modify pharmacotherapy regimen, HCRU, subject survey

✓ Visits can be conducted in person, virtually or over the phone

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1. BACKGROUND AND RATIONALE

1.1 Background

Early palliative care after diagnosis with incurable cancer improves quality of life (QOL) and may prolong overall survival [1-7]. However, there is large inter-individual variability in response to supportive care medications, such as those for pain and depression [6,8]. Pain affects more than 75% of cancer patients with advanced disease. Less than one-third of all patients achieve pain improvement with conventional strategies within one month of presentation [9]. Depression affects about one-third of cancer patients and has been linked to poorer prognosis and survival [10-13]. Pain, depression, and fatigue often coexist as a symptom cluster in cancer patients [14,15]. The combined effects of pain and depression is a significant public health crisis, particularly in the era of the opioid epidemic. Patients with moderate to severe depression are more than twice as likely to misuse opioids for non-pain symptoms compared to non-depressed patients [16]. Improper opioid prescribing has prompted the Center for Disease Control and Prevention (CDC) to issue guidelines for improving prescribing to mitigate abuse and addiction concerns [17]. Suboptimal management of cancer-related symptoms like pain and depression compromises potential cancer therapy benefits, disrupts clinic workflow, increases emergency room visits, and impacts patient satisfaction [18].

Pharmacogenomics (PGx) – the impact of genetic variation on drug response – is well documented [19] and can significantly impact response to supportive therapy, especially pain and depression medications [18,20]. Data suggests >90% of individuals carry a PGx variant contributing to drug response [21]. As this data grows along with more affordable analytic technology, it will soon be standard of care to perform routine PGx testing prior to treatment. The truest value of this data can only be fully realized when it is implemented preemptively into the routine workflow and embedded within care pathways, as discussed in previous reviews [21,22]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has thus far published approximately 45 drug-specific, peer-reviewed guidelines on how to best apply PGx to guide therapy (at least a dozen of which are related to supportive care medications) [23]; however, there is also an emerging level of relevant genes not currently covered by these guidelines. Effective integration of PGx-guided treatment pathways can help personalize medication selection in supportive oncology [18,20] and help determine the magnitude of drug-drug and drug-drug-gene interactions [24]. Several genes have been implicated with response to supportive care medications (Table 1).

Table 1. Summary of potential drug-gene interactions

Gene	Polymorphism(s)/variant(s)	Supportive care medications potentially affected
CYP3A4	*1B, *22	Oxycodone, hydrocodone, fentanyl, methadone
CYP3A5	*3, *6, *7	Oxycodone, hydrocodone, fentanyl, methadone
CYP2D6	*2, *3, *4, *5, *6, *9, *10, *17, *29, *41, duplications/copy number variations	Codeine, tramadol, oxycodone, hydrocodone, ondansetron, amitriptyline, imipramine, clomipramine, desipramine, doxepin, fluvoxamine, nortriptyline, fluoxetine, paroxetine, duloxetine, atomoxetine, amphetamines,
CYP2C9	*2, *3, *6, *8, *11	Diclofenac, ibuprofen, meloxicam, celecoxib, phenytoin
CYP2C19	*2, *3, *17	Esomeprazole, lansoprazole, omeprazole, pantoprazole, amitriptyline, citalopram, clomipramine, doxepin, escitalopram, imipramine, sertraline
CYP2B6	*4, *5, *6, *18	Methadone, bupropion, ketamine
COMT	Val158Met	All opioids
OPRM1	118A>G	All opioids
SLC6A4	Short or long allele	Selective Serotonin Reuptake Inhibitors
HTR2A	rs7997012	Citalopram

Opioid PGx: CYP2D6 activates codeine, tramadol, oxycodone, and hydrocodone to stronger opioids: morphine, o-desmethyltramadol, oxymorphone, and hydromorphone, respectively. CYP2D6 polymorphisms can significantly alter opioid pharmacology [25]. For example, codeine-related deaths reported in ultra-rapid metabolizers (UMs) resulted in a black-box warning recommending against its use [26-32]. Alternatively, poor metabolizers (PMs) may have ineffective analgesia due to impaired activation to morphine. Similar mechanisms are noted with tramadol, oxycodone, and hydrocodone [33-37]. CPIC recommends CYP2D6 UMs and PMs avoid codeine, tramadol, oxycodone and hydrocodone due to increased toxicity or lack of analgesia, respectively [38]. A base-pair substitution in the gene coding the mu-opioid receptor, OPRM1, can result in 60%–100% more morphine required for equal analgesia [39-41]. Analgesia can also be enhanced by presence of catecholamines, which are metabolized by the enzyme COMT. A base-pair substitution in COMT reduces enzyme activity by 3-4-fold, increases catecholamine exposure, increases opioid sensitivity, and lowers morphine equivalents required for analgesia, whereas those with higher activity may require at least doubling of the dose [39,42,43].

Antidepressant PGx: CYP2C19 metabolizes and inactivates citalopram, escitalopram, and sertraline. CYP2C19 PMs have increased toxicity risk with these medications, including QT prolongation [44,45]. Alternatively, UMs have lower plasma concentrations and increased risk of not responding [46]. CPIC recommends a 50% dose reduction in citalopram, escitalopram, and sertraline for CYP2C19 PMs and avoiding the drugs in UMs [47]. Paroxetine is primarily metabolized by CYP2D6; thus, PMs are at increased risk of adverse effects, particularly gastrointestinal [48,49], while UMs are at risk of poor drug response [50]. CPIC recommends avoiding paroxetine in CYP2D6 UMs and PMs [47]. Fluoxetine is metabolized by CYP2D6 and CYP2C19, thus similar mechanisms can influence drug response. Vortioxetine is primarily metabolized by CYP2D6 and the FDA label recommends a maximum dose of 10 mg/day in PMs [51]. Polymorphisms in the serotonin transporter gene, SLC6A4, and/or serotonin receptor gene, HTR2A, may result in reduced response to selective serotonin reuptake inhibitors. Randomized trials have

shown better clinical response with PGx-guided antidepressant selection [52-54] and tools have been developed to assist with PGx-based antidepressant prescribing [55,56].

PGx tests are now commercially available; however, due to their novelty, healthcare payors are reluctant to reimburse preemptive PGx screening and mandate further proof-of-concept and efficacy trials before coverage. Nonetheless, preemptive PGx testing increases the value proposition and prior studies suggest improved medication adherence and cost savings with PGx [57,58]. Further, many of the genes discussed earlier can affect non-oncology or non-supportive oncology medications that may be prescribed by other providers within the same health system (e.g., clopidogrel and CYP2C19). PGx results may be informative for management of other medications. Despite widespread availability of PGx tests and declining diagnostic costs, there is little data on the practicality of using PGx to improve supportive cancer care.

The Edmonton Symptom Assessment Scale (ESAS) (Appendix A) is a validated 10-item questionnaire assessing self-reported perceptions of pain, fatigue/energy, nausea, depression, anxiety, drowsiness, appetite, wellbeing, and shortness of breath. Each item is ranked from 0 to 10, with 10 representing the worst symptom. ESAS is routinely performed during all palliative medicine clinic visits. ESAS can be used to identify cancer patients presenting to palliative medicine with uncontrolled symptoms and can also be used to track symptom improvement or progression over time.

In a prior analysis we identified 46% of cancer patients at Levine Cancer Institute were prescribed a supportive care medication within 90 days of intake to the cancer hospital, mainly for pain (69%) and/or nausea (46%). Of these, 86% received at least one supportive care medication with PGx evidence and 84% received a CYP2D6-metabolized drug. Based on reported CYP2D6 allele frequencies conferring altered metabolism, 650 (20%) were expected to have altered drug response, suggesting preemptive PGx testing may have broad applicability in this population. PGx testing in this high-risk population may improve medication management and symptom control.

1.2 Study Rationale and Study Design

Over 90% of cancer patients experience cancer- or treatment-related symptoms, and at least 50% have uncontrolled symptoms throughout their lifetime. This significantly impacts patients' QOL, response to therapy, and potentially survival. Thus, guidelines recommend early palliative intervention for all cancer patients with advanced disease; however, many medications used to treat these symptoms are plagued with a system of trial and error, with prolonged time to symptom control or improvement.

Objective tools are needed to improve drug selection and reduce symptom burden. PGx allows for personalized medical decisions based on patient-specific genetics and provides a unique opportunity to reduce arbitrary drug selection and improve personalized prescribing. By studying the application of a PGx test to alter drug prescribing patterns for pain and depression and improve treatment outcomes in supportive cancer care, these results will provide critical information to understand the feasibility and utility of

performing preemptive, real-time PGx testing in a busy, outpatient clinic. This study will help shift supportive care prescribing paradigms from a trial-and-error approach to a personalized, genomics-driven method. Ultimately, using PGx to optimize medication selection and control cancer-related symptoms may improve QOL, as measured by aggregate ESAS scores, throughout the cancer care continuum, potentially extending overall survival.

We propose a prospective clinical trial of adult cancer patients at Levine Cancer Institute presenting to the Department of Supportive Oncology's palliative medicine clinic with moderate to high pain and depression (screened using ESAS at initial palliative medicine visit). Genotyping results will be returned within five business days. A PGx specialist will provide detailed clinical interpretations to the palliative medicine clinic and upload a copy of the results as well as a clinic note into the subject's medical chart. Each subject will also be counseled on their test results. A note will be placed in each subject's chart alerting the provider that the subject is on study and should be referred for pharmacy consultation to evaluate PGx test results prior to prescribing supportive therapy during the study period. The number of pharmacy consults for subjects undergoing PGx testing, type of medication recommendations, actionable genotypes, and rate of acceptance by the provider will be documented. Other data elements to be collected include all PGx test results, demographic data, medical/medication history, ESAS (Edmonton Symptom Assessment System) symptom scores, and PHQ9 (Patient Health Questionnaire) scores. The number and duration of emergency department visits and hospitalizations will be used to estimate health care utilization and costs. Subjects will complete a short survey at the end of the study period (from enrollment [day of the buccal swab] to the Final visit) regarding their knowledge about PGx, and whether access to PGx information improves satisfaction with care and communication.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Estimate the proportions of subjects undergoing PGx testing who receive at least one drug/dose selection or modification based on their test results within any of the study visits where PGx results are available.

2.1.2 Secondary Objectives

- Determine the impact of PGx on treatment outcomes by measuring pain scores using the Edmonton Symptom Assessment Scale (ESAS) (Appendix A) and depression scores using the Patient Health Questionnaire (PHQ) 9 (Appendix B) at study visits after the Baseline study visit. Symptom scores will also be compared between those receiving PGx testing and a matched control receiving clinical management alone.
- Describe subject perspectives (Appendix C) of PGx testing using a survey administered to subjects after/at the Final visit (or sooner if withdrawn).

2.1.3 Exploratory Objectives

- Determine the types & frequencies of actionable genotypes that result in drug/dose selection or modification(s) and those that do not result in drug/dose selection or modification(s).
- Describe the types of new medications prescribed (using medications of interest list; Appendix D) or medication/dose adjustments based on the PGx results.
- Determine the type & frequency of drug/gene interactions present at the Baseline and the Final study visit using CPIC guidelines and FDA's pharmacogenomics table.
- Summarize PGx best practice advisory alerts among participants enrolled after the transition to Epic to describe the proportion of participants that had a BPA fire in the EMR, the number and type of BPAs per participant, and any actions taken from the BPA.

2.2 Endpoints

2.2.1 Primary Endpoint

A binary variable will be recorded for each subject undergoing PGx testing to indicate whether or not the subject received at least one drug/dose selection or modification based on their test results at any study visit where PGx results were available.

2.2.2 Secondary Endpoints

- A count variable will be recorded for each subject undergoing PGx testing indicating the total number of drug/dose selections or modifications received across all study visits where PGx results were available.
- Pain scores assessed by the ESAS and depression scores using PHQ9 will be recorded for each subject at the Baseline and all the visits.
- Health care resource utilization (HCRU) and costs will be estimated based on the number of inpatient, emergency department, outpatient, and pharmacy encounters, among others, occurring one year prior to and during the study period.
- Discrete variables will be recorded to indicate subject survey responses.

2.2.3 Exploratory Endpoints

- Binary variables will be recorded for each subject, indicating the presence or absence of an actionable genotype for each of the tested genotypes.
- Discrete variables will be recorded for each subject indicating the new medications prescribed or medication/dose adjustments made using the PGx results.
- Discrete variables will be recorded for each subject indicating the drug/gene interactions present at the Baseline and at the Final study visit. A count variable indicating the number of interactions will also be recorded.
- PGx best practice advisory (BPA) alerts: BPA alerts are fired within Epic when there is presence of a drug-gene interaction at the time of medication order entry. The following will be determined for study participants enrolled after the transition to Epic: a binary variable indicating the presence of a BPA in their EMR and a count variable indicating the total number of BPAs in their EMR.

3. SUBJECT SELECTION

3.1 Subject Identification and Recruitment

Accrual is expected to be 80 eligible subjects. All patients will complete ESAS during a regularly scheduled visit to the Department of Supportive Oncology's palliative medicine clinic (Palliative medicine clinic). Potential candidates will be identified by reviewing the EMR to identify patients with ESAS pain ≥ 4/10 and/or depression ≥ 3/10 (or diagnosed with depression with a clinical need to adjust depression medications).

It is expected that 80 eligible subjects will be required to enroll 65 evaluable subjects. In the event that more subjects are required to achieve 65 evaluable subjects, subject enrollment will continue until 65 evaluable subjects have been enrolled.

Target accrual period of this study will be approximately 30 months.

3.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Written informed consent and HIPAA authorization for release of personal health information
2. Completion of ESAS at initial palliative medicine clinic visit, presenting with moderate to high pain (≥ 4/10) and/or depression (≥ 3/10) or diagnosed with depression with a clinical need to adjust depression medications identified by the provider.
3. New patients ≥ 18 years of age who have had either an initial visit in the Department of Supportive Oncology's palliative medicine clinic or a re-establishment of care visit with the last visit being at least 1 year prior to the date of consent, with hematologic malignancy or any stage solid tumor malignancy according to the provider. Patients without confirmation of malignancy at the time of enrollment can be enrolled based on radiographic evidence suggesting the likelihood of malignancy per investigator discretion.
4. Agree to at least one additional palliative medicine clinic visit per protocol.
5. Able to provide a buccal sample for PGx testing

3.3 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Psychiatric illness, social situations, or active/recent (within 30 days) history of illicit substance (e.g., cocaine, heroin) abuse that would limit compliance with study requirements (e.g., study visits, medication compliance, etc.) as determined by the Investigator.
2. Patients who have had prior multiple visits in palliative medicine clinic less than one year prior to consent.
3. History of prior allogeneic stem cell transplant or liver transplant

3.4 Subject Withdrawal

Subjects MAY be withdrawn from the study for the following reasons:

- More than 8 weeks pass between the completion of ESAS and the Baseline study visit.
- Subject withdraws consent from study procedures. A subject will be removed from the trial at his/her own request. At any time during and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantages as a result.
- If, in the Investigator's opinion, compliance with study procedures is compromised and affects the integrity of the trial.
- Death.

Subjects MAY be withdrawn from the study for the following reasons:

- The subject is unable to undergo one or more study visits.
- Use, or suspicion of use, of illicit drugs or substances (i.e., positive urine drug screening) that may, in the opinion of the Investigator, have a reasonable chance of contributing to medication non-compliance
- Developing a concurrent illness or situation that would, in the Investigator's judgment, significantly affect assessments of clinical status and trial endpoints.
- DNA from buccal swabs is not viable, and the laboratory cannot perform PGx testing. Subjects may be asked to provide additional swabs if recollection performed no later than one week prior to the Baseline study visit.

Any subject removed from the trial will remain under medical supervision per standard of care procedures until discharge or transfer is medically acceptable.

3.5 Screen Failures

A subject who, for any reason (e.g., failure to satisfy the eligibility criteria or withdraws consent), terminates his/her study participation before being enrolled to the study is regarded as a screen failure. All screen failures will be tracked. Reasons for screen failure (e.g., specific inclusion/exclusion criteria not met) will be recorded in the CTMS/Subject Console.

4. REGISTRATION

4.1 Sequence Number Assignment

Following informed consent, subjects will be registered by the LCI Data Coordinating Center and assigned a Sequence Number.

The study intervention (PGx testing) is not blinded to the subject or the Investigator.

5. STUDY PLAN

The study design is a prospective interventional clinical trial designed to investigate the application of PGx testing to personalize cancer symptom management, particularly pain and depression.

Potential candidates will be presented with consent; screening data for these patients, including ESAS symptom scores, will be captured and used for analysis (Section 11.4.5). A full waiver of consent and HIPAA for data collection will be requested for the control cohort, which includes patients (with pain ≥ 4/10 and/or depression ≥3/10 who have not been presented with consent and who were presented with consent but decline participation in the study (i.e., do not consent). Study subjects who consent and subsequently screen fail for any reason will also be included in the control cohort. Patients who agree will undergo the informed consent process, and subjects who consent will be screened for eligibility. Those meeting eligibility criteria will be enrolled and undergo buccal swab collection. **Enrollment day** will be considered at the **buccal swabs collection day**. If the collected buccal swabs do not contain enough viable DNA for PGx testing, subjects may be asked to provide additional swabs. No less than 2 weeks and no more than 8 weeks should pass between the first ESAS completion and the date of the **Baseline study visit**. **The Baseline study visit** may be completed during a clinic visit (in person or virtually) or over the phone. It is estimated that PGx results will be available within five business days of swab receipt by the laboratory, and a detailed report will be sent to the clinic. A copy of the test results in PDF (Portable Document Format) format and PGx consultation note will be uploaded to the subject's medical chart. Apart from the availability and use of PGx test results to guide pharmacotherapy, subjects will receive standard of care treatment and undergo ESAS screening during the palliative medicine visits. PHQ9 will be collected by the research team electronically, during the study visit by paper, or by phone. Data, including symptom scores and medications, at each visit, will be captured until the **Final study visit**. Subjects will be asked to complete a short survey within 30 days after the Final study visit to assess their perspectives on PGx testing and the care they received (administered preferably electronically, alternatively via paper during the Final visit at a clinic or over the phone).
Subjects presenting with depression score 3 or greater and/or experiencing depressive symptoms during the clinical trial are highly encouraged to receive treatment in the LCI psycho-oncology clinic.
Subjects will be offered the option to complete study visits during a clinic visit (in-person or virtually) or over the phone.
Subjects will not be reimbursed for study participation; however, they will receive PGx testing at no cost and will receive a full copy of their test results at their request.

5.1 Study Intervention and Pharmacogenomics Testing

- After obtaining the informed consent, two buccal swabs will be collected at least one week prior to the Baseline study visit (the next palliative medicine visit after informed consent). Buccal swabs may be collected by the subject at home or on site.
- Buccal swabs will be transferred to the Levine Cancer Institute's Molecular Biology Laboratory on the same or following day of collection for DNA extraction and genotyping. Subjects who collect samples at home will be instructed to collect and ship overnight only on Monday through Thursday (samples should not arrive at the lab on the weekend or on holiday).
- Genotyping will occur at the Molecular Biology Laboratory for polymorphisms in candidate genes potentially related to pain and depression medications.
- Raw data will feed into an online HIPAA compliant web portal for translation of results into genotype-phenotype data. Each test result will be reviewed by the lab for accuracy of

results and quality control. The laboratory director and/or Sponsor-Investigator (S-I) or sub-investigator if S-I is not available will approve final genotype calls.

- Pharmacists will interpret genotype and phenotype results and translate PGx results into actionable prescribing decisions. Guidelines, including CPIC (https://cpicpgx.org/) and FDA (https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations), and clinical judgment will be used to make medication recommendations. A test report will be developed for each subject. The pharmacist will send a copy of the report to the referring provider and upload a copy into the medical chart along with a PGx consultation note.
- Subjects will continue to receive supportive care and undergo scheduled study visits throughout the study. Changes to medications can be made during scheduled study visits, on-call visits, or virtually over the phone to mimic standard practice. Providers will be encouraged to refer all study subjects requiring pharmacologic intervention for pharmacy consultation to evaluate PGx results prior to drug prescribing. However, this is not protocol-mandated, and a deviation will not occur if a provider modifies treatment regimens without consulting the pharmacist. The number of pharmacy consults, types of medication recommendations, actionable genotypes, and acceptance rate by the provider will be documented. Data will be collected up to the completion of the Final visit.

5.1.1 Schedule of Clinic Assessments

Every visit can occur during a clinic visit (in-person or utilizing virtual care) or over the phone. A subject can be assessed by a trained and delegated Palliative care provider, PharmD, study coordinator, or RN:

- Baseline (day 0) study visit should be no earlier than 2 weeks and no later than 8 weeks from the first ESAS completion.
- A total of 3 subsequent study visits and the Final visit will occur every 4 weeks (± 1 weeks) after the Baseline visit. Additionally, non-protocol-directed visits may occur on an as-needed basis (e.g., an emergency due to uncontrolled symptoms).

5.1.2 Symptom Assessment Tools

- ESAS (Appendix A) is a 10-item questionnaire assessing self-reported perceptions of pain, fatigue/energy, nausea, depression, anxiety, drowsiness, appetite, wellbeing, and shortness of breath. Each item is ranked from 0 to 10, with 10 representing the worst symptom. ESAS is routinely performed during all palliative medicine clinic visits.

- PHQ9 (Appendix B) is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. PHQ9 incorporates depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. PHQ9 scores of 0-4 indicate normal or no depression, 5-9 mild, 10-14 moderate, 15-19 moderately severe, and 20-27 severe depression. PHQ9 will be collected for this study, preferably electronically, within 2 business days prior to the study visit or by phone call within 2 business days prior to the study visit. Alternatively, PHQ9 can be collected during a clinic visit on paper.

5.1.3 Subject Survey (Appendix C)

The patient survey is intended to assess the subject's perspective of pharmacogenomics testing. The survey will be administered preferably electronically, alternatively over the phone or on paper during a clinic visit at the Final visit time-point or sooner if withdrawn.

If data from ESAS, PHQ9 questionnaires, and Subject survey are missing, when possible, the reason for the missing data will be categorized and documented as follows:

- the subject felt too ill;
- clinician or nurse felt the subject was too ill;
- the subject felt it was inconvenient or took too much time;
- the subject felt it was a violation of privacy;
- the subject didn't understand the actual language or was illiterate;
- administrative failure to distribute the questionnaire;
- other, specify;
- unknown.

6. STUDY CALENDAR

6.1 Table 2. Study Procedures and assessments

Study Procedures	Registration	Baseline[1,3]	Study Visits[2,3]	Final Visit[2,3]
Informed Consent	X			
Subject demographics[4]		X		X
Buccal swab collection for genotyping	X[5]			
Medical/treatment history[6]		X		
Drug allergies[7]		X	X	X
PHQ9[8]		X	X	X
ESAS[9]	X[10]	X	X	X
Medication list[11]		*Continuously throughout the study from the Baseline to the Final visit*		
Document use of PGx test results[12]				
Document use of healthcare resource utilization (HCRU)[13]				
Final visit survey[14]				X

[1]The Baseline study visit should be completed no earlier than 2 weeks and no later than 8 weeks from the first ESAS completion.
[2]A total of 3 subsequent study visits will occur every 4 weeks (± 1 week) after the Baseline visit. The Final study visit will occur 4 weeks (± 1 week) after the third completed Study Visit. Subjects will be offered the option to complete study assessments during a clinic visit (in person or virtually) or over the phone.
[3]All the study visits and assessments (including the Baseline visit) can occur during a clinic visit (in-person or utilizing virtual care) or over the phone. Study visits/assessments may be performed by a trained and delegated provider, RN, research coordinator or Pharm D.
[4]Demographics collected during the Baseline visit will be race, ethnicity, insurance status, and zip code. Demographics collected on the Final visit will be annual household income and education level.
[5]Buccal swab collection (Enrollment day) should be performed no later than one week prior to the Baseline study visit (second palliative medicine visit) at the clinic or the subject' home. The specimen may be obtained the same day after the informed consent is signed.
[6]Medical/treatment history: cancer type, stage of disease, ECOG performance status, active chemotherapy, surgery, and radiation therapy within 30 days of the Baseline visit.
[7]Only to medications listed in Appendix D
[8]Research team will collect PHQ9 prior to the study visit, preferably electronically or by phone, within 2 business days and send them to the Supportive Oncology provider and Sponsor-Investigator. If the response for the PHQ9 question #9 is anything greater than 0, a research designee will contact the applicable LCI social worker. Alternatively, PHQ9 can be collected during clinic visits on paper.
[9]ESAS will be obtained during a clinic visit or utilizing virtual care.
[10]ESAS score done historically visit per standard of care at the initial palliative medicine visit will be collected in the dataset and used for analysis (Section 11.4.5)
[11]Medications listed in Appendix D, currently taken and/or newly prescribed during the visit, and other drugs and/or drug modifications recommended by the pharmacist or provider based on PGx test results outside those in Appendix D list will be collected every study visit.
[12]Use of PGx test results should be documented any time a drug/dose modification is made (during palliative medicine visits or in between visits).
[13]HCRU (defined as any encounter classified as an outpatient (OP), inpatient (IP), or emergency department (ED) encounter) occurring during the study period will be collected by a research designee. Each encounter will be counted as unique per classification. IP encounters that result from an emergency department presentation will be classified as both an ED encounter and IP encounter. Any encounter lasting longer than 24 hours will be considered an IP encounter. Insurance status and/or type and reason for presentation at each encounter will also be collected.
[14]Survey will be preferably administered electronically (distributed to the subject`s email within 30 days after the Final visit). Alternatively, a research designee can collect a survey via paper during the Final visit at the clinic (or sooner if withdrawn) or over the phone as an option.

7. DETAILS ON STUDY PROCEDURES

Please also refer to the Study Calendar in Section 6.

7.1 Registration procedures

- Informed consent
- Buccal swab collection should be performed no later than one week prior to the Baseline study visit

7.2 Baseline Procedures

Baseline study visit should be completed no earlier than 2 weeks and no later than 8 weeks from the first ESAS completion during the clinic visits or utilizing virtual care.

- Subject demographics: Race, Ethnicity, Work Status, Insurance Status, Zip code
- Medical history: data related to disease and/or diagnosis, including cancer type, stage of disease, and ECOG performance status
- Treatment history: therapeutic interventions including surgery within 30 days of Baseline, active chemotherapy, active radiation, and active supportive care therapy
- Drug allergies to medications listed in Appendix D
- ESAS Appendix A collected as a SOC
- PHQ9 Appendix B collected preferably electronically within 2 business days prior to the study visit, or alternatively on paper during the clinic visit or by phone call within 2 business days prior to the study visit
- Medications listed in Appendix D, currently taken at the time of Baseline study visit and/or newly prescribed during the visit and, other drugs and/or drug modifications recommended by the pharmacist or provider based on PGx test results outside those in Appendix D
- Use of PGx to guide/modify pharmacotherapy regimen
- HCRU

7.3 Study Visits

- A total of 3 subsequent study visits will occur every 4 weeks (± 1 week) after the Baseline visit.
- During *each* study visit (in a clinic or virtually), the following information will be collected:
  - Drug allergies to medications listed in Appendix D
  - ESAS Appendix A collected as a SOC
  - PHQ9 Appendix B collected preferably electronically within 2 business days prior to the study visit, or alternatively on paper during the clinic visit or by phone call within 2 business days prior to the study visit
  - Addition or change in medications listed in Appendix D, and/or dosages, and other drugs and/or drug modifications recommended by the pharmacist or provider based on PGx test results outside those in Appendix D
  - Use of PGx to guide/modify pharmacotherapy regimen
  - HCRU

7.4 Final Visit

- The Final study visit will occur 4 weeks (± 1 week) after the third completed Study Visit.
  - Drug allergies to medications listed in Appendix D
  - ESAS Appendix A collected as a SOC
  - PHQ9 Appendix B collected preferably electronically within 2 business days prior to the study visit, alternatively via paper during a clinic visit or by phone call within 2 business days prior to the study visit
  - Addition or change in medications listed in Appendix D and/or dosages, and other drugs and/or drug modifications recommended by the pharmacist or provider based on PGx test results outside those in Appendix D
  - Use of PGx to guide/modify pharmacotherapy regimen
  - HCRU
  - Patient survey (Appendix C)
  - Subject demographics (part of the final survey): annual household income and education level.

7.5 Correlative Study Procedures

Correlative specimens for this study include buccal swabs for DNA extraction and genotyping for germline pharmacogenes to be analyzed per Section 5.1. After obtaining informed consent, two buccal swabs will be collected by the research designee. No processing of samples is required prior to transfer. The samples will be transferred to the Levine Cancer Institute Molecular Biology Laboratory for DNA extraction and genotyping.

7.5.1 Source and Timing of Biospecimen Collections

All buccal specimens will be obtained after informed consent no later than one week before the Baseline study visit. The specimen may be obtained the same day as informed consent. The research designee will instruct the subject on the appropriate buccal swab collection.

Either the research staff member or the subject can perform the swabbing, depending on subject preference. Subjects will be given the option to collect buccal swabs at home, in which case a buccal collection kit with instructions on collection and shipping will be mailed to the subject. Subjects will be asked to collect buccal swabs and ship within 48 hours, ideally (max 96 hours) of receiving the buccal swab kit.

All samples collected on site will be transported by either research or laboratory staff at ambient temperature to the Molecular Biology Laboratory at the Levine Cancer Institute. Samples collected by the subject at home will be mailed at ambient temperature directly to the Molecular Biology Laboratory. Samples will be logged in and processed for DNA extraction and genotyping per laboratory procedures.

7.5.2 Storage of Biospecimens

Specimens will be stored in the Molecular Biology Laboratory only until the pharmacogenomic results have been confirmed by both the Laboratory Director and Sponsor-Investigator (approximately one week from sample receipt). Once PGx results are confirmed by the Laboratory Director and Sponsor-Investigator, all samples will be discarded according to laboratory procedures.

8. REMOVAL OF SUBJECTS FROM STUDY

8.1 Off Study

Subjects are considered Off Study after completion of the subject survey and the Final visit that occurs 4 weeks (± 1 week) after the third completed Study Visit.

Subjects may stop their participation in this study at any time if they no longer wish to participate or if the Investigator believes this to be in the best interest of the subject.
When subjects are removed from the study, the reason for study removal and the date the subject was removed should be documented. Other reasons a subject may be removed from study include, but are not limited to:

- Subject non-compliance with study participation, in the opinion of the Investigator
- The subject or legal representative withdraws study consent
- The subject's tumor is confirmed to be a benign per provider
- Buccal swab collected and shipped more than 96 hours after receiving the buccal swab kit or if otherwise deemed non-viable
- The subject unwilling to recollect the buccal swabs if DNA from the first buccal swabs is not viable
- The subject is lost to follow-up
- Investigator's decision to withdraw the subject
- Subject death

Subjects that are Off Study will not participate in any study- related procedures, including data collection.

9. DATA AND SAFETY MONITORING PLANS

Data will be collected in electronic case report forms (eCRFs). The database uses fully validated secure web-enabled software that conforms with 21CFR Part 11 requirements. Study personnel will be trained on data entry by the sponsor and provided protocol-specific eCRF guidelines.

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies, the protocol-specific monitoring plan and will abide by applicable regulations and guidelines (e.g. Good Clinical Practice [GCP]). The Sponsor-Investigator and other sponsor-level team members will meet regularly to monitor subject consents, enrollment and retention, safety data, and timeliness/validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit reports to the

LCI Data and Safety Monitoring Committee according to the institutional Data and Safety Monitoring Plan.

This study will be monitored to ensure the study is conducted in compliance with the study protocol, SOPs of the LCI and Atrium Health Office of Clinical and Translational Research (and/or other participating institutional SOPs), the FDA, and other applicable regulations and guidelines (e.g. GCP).

Investigators and/or their delegated study personnel will be required to be available during the monitoring visits.

10. POTENTIAL RISKS/UNANTICIPATED PROBLEMS

10.1 Potential Risks

There is no investigational treatment as part of this clinical trial. All supportive care treatments are considered standard of care. The primary intervention is PGx testing. The potential risks are limited to those associated with subject confidentiality, specimen collection, and knowledge of PGx test results. Nonetheless, the American College of Medical Genetics has deemed PGx testing as low risk since these genes are not related to disease susceptibility or prognosis.

10.1.1 Subject Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies on subject privacy and HIPAA and that the investigator and other site personnel will not use such data and records for any purpose other than conducting the study. We do not anticipate any breach of confidentiality as no records will be shared with any personnel outside the research team. All medical information, including assessments and other medical records will be recorded and stored in a database. The databases will exist on a password protected secured server. Medical records data will be abstracted by the Research Designee. All records will be kept confidential.

Pharmacogenomic test results will be added to each subjects' Electronic Medical Record. Subjects will be provided a copy of his/her pharmacogenomic test results at their request, which can be used for other clinical/medication decisions downstream. The subject is free to share this information with anyone.

10.1.2 Biomarker Specimen Collection

Buccal Swabs
No adverse events are expected for buccal swab procedures. If a subject has an unexpected adverse event, the Investigator will treat the subject according to standard of care practices until the adverse event resolves.

Adverse events will not be recorded for the purposes of this study but will be a part of the subject's medical record as per standard operation procedures.

10.1.3 Emotional Distress

Some questions in the questionnaires could create emotional distress or confusion. If a subject experiences distress or confusion, the questionnaire process will be interrupted or discontinued, and the Research Designee will follow-up with the Sponsor-Investigator. Knowledge of PGx test results may result in emotional distress; however, the American College of Medical Genetics have identified pharmacogenes as "low risk" as they are not related to hereditary disease conditions, but rather how a person may metabolize or process various medications. There is a low likelihood of emotional distress caused by knowledge of PGx information. All subjects will be counseled on their test results by a trained pharmacist.

10.2 Unanticipated Problems (UAP)

10.2.1 Definition

A UAP is any incidence, experience or outcome that is unexpected (e.g., a lost or stolen laptop computer that contains sensitive study information) given the information provided in research-related documentation (e.g., informed consent) and the study population characteristics, that is related or possibly related to participation in the research study and places the participant at an increased risk.

10.2.2 Reporting

All UAPs occurring during the conduct of a protocol and meeting the definition of a UAP will be reported to the IRB per IRB reporting requirements.

11. STATISTICAL CONSIDERATIONS

11.1 Milestones

Registration Date: Date of consent

Enrollment Date: Date the buccal swab is collected.

Off Study: Date of the Final visit that occurs 4 weeks (± 1 week) after the third completed Study Visit.

11.2 Sample Size and Accrual

Enrollment to the study will continue until 65 evaluable subjects have been identified (Section 11.3).

We anticipate enrolling 80 eligible subjects, of which we estimate 65 will be evaluable (defined in 11.3). With this sample size, the width of the 95% Clopper-Pearson confidence interval will be ≤25%, regardless of the observed DDSM rate.

11.3 Analysis Populations

Analyses of the primary objectives and secondary objectives concerning counts of PGx-guided drug/dose selections or modifications based on their test results will be conducted on the evaluable population, defined as the population of enrolled subjects with confirmed malignancy (per provider documentation) and completing at least one study visit where PGx results are available (including the baseline visit).

Analyses of secondary objectives concerning the impact of PGx on pain and depression scores will be conducted on the primary evaluable population with valid pain and/or depression scores for at least one post-Baseline Study visit.

Analyses of secondary objectives concerning health care utilizations, costs, and subject survey responses and all exploratory objectives will be conducted on all enrolled subjects.

11.4 Analysis Methods

11.4.1 Timing of Analysis

Final analysis will occur after all subjects have completed their Final visit or otherwise have come off study.

11.4.2 Subject Disposition

A summary of all consenting subjects will be provided at the end of the study. This will include those that consented, enrolled, screen failed, died, were lost to follow-up or withdrew consent.

11.4.3 Baseline Subject Characteristics

A summary of subject demographics will be completed.

11.4.4 Primary Analysis

The proportion (the denominator being the number of evaluable subjects) of evaluable subjects undergoing PGx testing and receiving at least one drug/dose selection/modification based on their test results at any study visit where PGx results are available will be calculated, alongside 95% Clopper-Pearson confidence intervals.

11.4.5 Secondary Analysis

Total counts and descriptive statistics of the number of drug/dose selection/modifications made due to subject PGx test results at all visits where PGx results are available will be summarized.

A single-arm analysis for the PGx cohort will be performed: Descriptive statistics of ESAS pain scores and PHQ-9 depression scores will be calculated and summarized at study visits. Repeated-measures linear mixed models will be estimated for pain and depression, separately, adjusted for baseline clinicodemographic characteristics and include a main effect for time and a random effect for subject.

The following analysis will be performed for both the PGx and control cohorts:

A matched analysis for ESAS pain and depression scores will be carried out, comparing the study cohort to a matched cohort of unique patients receiving clinical management alone during the same time period the trial is enrolling. Standard-of-care patients with ESAS pain ≥4 and/or depression scores ≥3 at their first visit to the palliative medicine clinic or a re-establishment of care visit with the last visit being at least 1 year prior—these visits occurring within the same time period the trial is enrolling—will be identified and considered in the matched analysis.

Enrolled subjects will be matched to a similar case in cohort by:

- ESAS pain and depression symptom scores at first visit to palliative medicine clinic (i.e., study screening for study cohort)
- Age
- Sex
- Race
- Clinic visit schedule.

Between-group comparisons of those study subjects and control patients will be performed estimating repeated-measures linear mixed models for pain and depression, separately, to estimate the effect of PGx testing (i.e., treatment effect) on symptom scores adjusted for baseline clinicodemographic characteristics, a main effect for treatment, for time, an effect for treatment by time interaction, and a random effect for subject.

Additionally, the average post-baseline symptom score will be calculated for each individual (separately for pain and depression). The distributions of the average post-baseline symptom scores will be compared between the cohorts using analysis of variance techniques with adjustments for clinicodemographic characteristics.

Health care utilization (e.g., instances of participant presenting at an emergency department, admitted as an inpatient, any outpatient encounter, or medication prescription) and reason for encounter will be assessed during the study period (starting on the Baseline to the Final study visit) for those undergoing PGx testing. HCRU in year prior to start of study enrollment will be collected for patients from institutional enterprise data warehouse (EDW) via raw billing and medical record data. Insurance status and/or type at each encounter will also be collected. An encounter resulting from another (e.g., ED presentation leading to IP) will be counted separately. Any ED encounter lasting longer than 24 hours will be considered an IP encounter. Diagnosis and procedure codes and priority sequence numbers will be collected from the EDW at least 6 months following study closure to allow for final bills to accrue for HCRU encounters, for those that underwent PGx testing and matched controls. Diagnosis and procedure codes used in billing for each encounter will be used to estimate institutional costs or reimbursement and/or to publicly available sources (e.g., CMS fee schedule) and to obtain patient's historical prescription drugs. Endpoints will be summarized by encounter-level and patient-level data files for frequency of HCRU and descriptive analysis of associated cost. Once data files have been constructed, data will be fit to appropriate statistical analyses and multivariate regression will be employed to interrogate the relationship between costs, resource utilization PGx results, sociodemographic, and clinical patient characteristics. Sensitivity and scenario analyses will be conducted to assess the robustness of model estimates.

Subject responses to survey tool administered at the Final visit (or sooner if withdrawn) will be summarized and described. Regression models may be estimated to describe the association of response and responder characteristic, both univariately and multivariately, adjusted for relevant baseline characteristics.

11.4.6 Exploratory Analysis

- Frequencies of actionable genotypes that guide drug/dose selection or modification will be summarized and described alongside types of mutations/phenotypes for each of the test genotypes.
- New medications prescribed and medication/dose adjustments based on PGx results will be summarized and described by frequencies of specific medication or medication classes prescribed and types of medication dose/adjustments, respectively.
- Drug/gene interactions present on the Baseline and the Final study visit will be grouped, summarized, and described qualitatively. Additionally, summary statistics of the numbers of interactions will be calculated.
- Calculate the following:
    - The proportion and 95% CI (using the Clopper-Pearson method) of PGx best practice advisory alerts that fire in Epic across all prescriptions across participants enrolled after the transition to Epic.

- The proportion and 95% CI (using the Clopper-Pearson method) of PGx best practice advisory alerts that fire in Epic across all new prescriptions within each participant enrolled after the transition to Epic.
- The proportion and 95% CI (using the Clopper-Pearson method) of actions taken from PGx best practice advisory alerts in Epic among all alerts fired across study participants enrolled after the transition to Epic.

12. STUDY COMPLETION OR TERMINATION

12.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have withdrawn from the study
- All subjects have discontinued from the study
- The IRB, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cutoff date

12.2 Termination

The study will be terminated when one or more of the following conditions occur:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g., UAPs)
  - Results of parallel clinical studies
  - If the study conduct (e.g., recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame
- The Sponsor-Investigator has decided to close the trial at any site and at any time

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow- up, must be taken care of in an ethical manner.

13. STUDY MANAGEMENT

13.1 IRB Approval

The final study protocol and the final version of the informed consent form(s) must be approved in writing by the Sponsor IRB.

The Sponsor-Investigator is responsible for informing the Sponsor IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB annually, as local regulations require.

13.2 Informed Consent

Before recruitment and enrollment onto this study, the potential subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

13.3 Protocol Adherence

Except for an emergency situation in which proper care for the protection, safety and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.4 Changes to the Protocol and/or Informed Consent

13.4.1 Amendments to the Protocol

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol (amended protocol) and/or the revised informed consent must be approved by the Sponsor-Investigator and the Sponsor IRB.

13.5 Protocol Deviations

If a deviation occurs, the event should be reported to the Sponsor-Investigator promptly. Any IRB reportable event that occurs must be reported to the IRB per institutional policies and reported to the Sponsor-Investigator as soon as possible.

NOTE: Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the IRB per IRB reporting requirements.

13.6 Retention of Records

Essential documentation (e.g., informed consents), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

13.7 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by GCP guidelines. The study will also be carried out in full conformity with Regulations for the Protection of Human Subjects

of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g., IRB) will be obtained for all participating centers before the start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigators may not modify or alter the procedures described in this protocol. The Sponsor-Investigator is responsible for the conduct of the trial at the sites in accordance with Title 21 of the CFR and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

13.8 Confidentiality of Records

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

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15. APPENDIX A. EDMONTON SYMPTOM ASSESSMENT SCALE

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

16. APPENDIX B. PATIENT HEALTH QUESTIONNAIRE (PHQ) 9

Protocol: LCI-SUPP-NOS-PGx-001 Date_____ Study Sequence ID

Initials

DOB

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

17. APPENDIX C. PGX PATIENT SURVEY

Protocol: LCI-SUPP-NOS-PGx-001

PGx Survey

Date:_____ ***Subject identifier***

Pharmacogenomics *is the study of how one's genetic makeup (i.e. their DNA) influences response to medications. Pharmacogenetic testing may identify changes in genes that control how one processes (e.g. metabolizes) medications in their body. These results may be useful in identifying whether someone might respond differently to a specific medication.*

1. What is your educational level?

   Less than high school degree High school degree or equivalent Some college but no degree

   Associate degree Bachelor`s degree Graduate degree Prefer not to answer

2. What is your annual household income?

   $0 - $15,000 $15,001 - $30,000 $30,001 - $45,000 $45,001 - $60,000

   $60,001 - $75,000 $75,001 - $90,000 More than $90,000 Prefer not to answer

3. Had you heard about pharmacogenetic testing prior to participating in this study?

   Yes No

4. Did you understand the purpose of pharmacogenetic testing before this study?

   Yes No Never heard of it

5. Did you understand the purpose of pharmacogenetic testing after enrolling on this study?

   Yes Somewhat No

6. How comfortable are you with understanding your pharmacogenetic test results?

   Very comfortable Somewhat comfortable Not comfortable

7. Do you think your results were or will be useful for managing your medications?

   Very likely Somewhat likely Not likely

8. How satisfied are you with communication of your test results by the clinic staff?

   Very satisfied Somewhat satisfied Not satisfied

9. Overall, are you satisfied with the care you received as part of this study?

   Very satisfied Somewhat satisfied Not satisfied

10. Would you recommend pharmacogenetic testing to a family member/friend?

    Very likely Somewhat likely Not likely

11. After learning about pharmacogenetics, what would you be willing to pay for testing?

    $200 $300 $400 $500 I would not pay for pharmacogenetic testing

Research designee name:_____

18. APPENDIX D. MEDICATIONS OF INTEREST LIST

Generic Name

Allopurinol
Alprazolam
Amitriptyline
Amphetamine
Aprepitant
Aripiprazole
Atomoxetine
Brivaracetam
Bupropion
Carbamazepine
Carvedilol
Celecoxib
Cevimeline
Citalopram
Clomopramine
Clonazepam
Clopidogrel
Codeine
Desipramine
Desvenlafaxine
Dexamethasone
Dexlansoprazole
Dextromethorphan/quinidine
Diazepam
Diclofenac
Donepezil
Doxepin
Dronabinol
Duloxetine
Efavirenz
Escitalopram
Esomeprazole
Fentanyl
Fluoxetine
Fluvoxamine
Fosphenytoin
Gabapentin
Granisetron
Hydrocodone
Hydrocodone/acetaminophen
Hydromorphone
Ibuprofen
Imipramine
Ketamine
Lansoprazole
Lorazepam
Meloxicam
Methadone
Methylphenidate
Metoclopramide
Metoprolol
Mirtazapine
Modafinil
Morphine sulphate
Nortriptyline
Olanzapine
Omeprazole
Ondansetron
Oxycodone, oxycodone hcl
Oxycodone/acetaminophen
Palonosetron
Pantoprazole
Paroxetine
Phenytoin
Pregabalin
Prochlorperazine
Propafenone
Rabeprazole
Sertraline
Simvastatin
Tacrolimus
Tamoxifen
Tapentadol
Temazepam
Tolterodine
Tramadol
Trazodone
Venlafaxine
Voriconazole
Vortioxetine
Warfarin
Zolpidem