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Design and Rational for the Precision Medicine Guided Treatment for Cancer Pain Pragmatic Clinical Trial

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Abstract

Introduction—Pain is one of the most burdensome symptoms associated with cancer and its treatment, and opioids are the cornerstone of pain management. Opioid therapy is empirically selected, and patients often require adjustments in therapy to effectively alleviate pain or ameliorate adverse drug effects that interfere with quality of life. There are data suggesting *CYP2D6* genotype may contribute to inter-patient variability in response to opioids through its effects on opioid metabolism. Therefore, we aim to determine if *CYP2D6* genotype-guided opioid

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prescribing results in greater reductions in pain and symptom severity and interference with daily living compared to a conventional prescribing approach in patients with cancer.

Methods—Patients with solid tumors with metastasis and a self-reported pain score 4/10 are eligible for enrollment and randomized to a genotype-guided or conventional pain management strategy. For patients in the genotype-guided arm, *CYP2D6* genotype information is integrated into opioid prescribing decisions. Patients are asked to complete questionnaires regarding their pain, symptoms, and quality of life at baseline and 2, 4, 6, and 8 weeks after enrollment. The primary endpoint is differential change in pain severity by treatment strategy (genotype-guided versus conventional pain management). Secondary endpoints include change in pain and symptom interference with daily living.

Conclusion—Pharmacogenetic-guided opioid selection for cancer pain management has potential clinical utility, but current evidence is limited to retrospective and observational studies. Precision Medicine Guided Treatment for Cancer Pain is a pragmatic clinical trial that seeks to determine the utility of *CYP2D6* genotype-guided opioid prescribing in patients with cancer.

Keywords

pharmacogenetic; CYP2D6; genotype; opioid; oxycodone; cancer; pain; patient reported outcome; symptom; trial design

Introduction

Approximately 60% of patients with cancer and up to 80% with metastatic disease report pain. (1, 2). Accumulating evidence suggests that survival is linked to pain management and other palliative support measures that improve quality of life.(3) Opioids are the cornerstone of therapy for most patients to relieve moderate to severe pain, with oxycodone and morphine considered first-line treatment options.(4) Unfortunately, only one-third of patients with cancer pain report decreased pain after 1 month of opioid therapy, while one-fifth have increased pain, and many patients experience reduced quality of life due to unrelieved pain, opioid side effects, or both; 30% undergo opioid rotation to find relief.(5, 6)

Although causes are multifactorial, there is evidence of a hereditary basis for inter-individual differences in pain sensitivity and opioid analgesia.(7, 8) The *CYP2D6* enzyme biotransforms select opioids (e.g. codeine, tramadol, oxycodone, hydrocodone) to metabolites with greater affinity for the μ -opioid receptor than the parent compound. (9, 10)

The *CYP2D6* gene is highly polymorphic, with over 100 alleles defined. Functional variation within *CYP2D6* includes single nucleotide polymorphisms (SNP), insertions, deletions, and instances where the gene is deleted, duplicated or multiplied. Individuals with no functional alleles are deemed poor metabolizers (PMs) and have little to no active *CYP2D6* enzyme. Intermediate metabolizers (IMs) have one loss-of-function allele and one reduced function allele and significantly impaired enzyme activity compared to normal metabolizers (NMs), which have at least one fully functional allele or two partially functioning alleles. (11) Pharmacokinetic studies have shown lower concentrations of active metabolites of codeine (morphine), tramadol (O-desmethyltramadol), oxycodone (oxymorphone), and hydrocodone (hydromorphone) in *CYP2D6* PMs compared to NMs. (9,

10, 12–14). Studies have further shown that lower active metabolite concentrations in PMs lead to decreased analgesia compared to NMs.(15, 16) On the other hand, ultra-rapid metabolizers (UMs), with multiple gene copies, are at increased risk for adverse drug effects, including life-threatening toxicities, compared to NMs.(13)

The Clinical Pharmacogenetics Implementation Consortium (CPIC) developed guidelines for interpreting and translating *CYP2D6* genotype information into prescribing decisions for codeine. The guidelines recommend considering an alternative opioid for *CYP2D6* PMs and UMs, making note that tramadol, oxycodone, and hydrocodone are not good alternatives because their metabolism is affected by *CYP2D6* activity. For IMs, the guidelines recommend to monitor codeine use for response.(11) While codeine is not commonly prescribed for cancer pain, oxycodone, hydrocodone, and tramadol are used commonly in this population, and oxycodone is a first line choice for prescribers at our institutions. Despite the evidence that *CYP2D6* genotype plays an important role in the pharmacokinetics and clinical response to opioids, there is a paucity of data on whether incorporating *CYP2D6* genotype information into opioid prescribing decisions improves pain management.(10, 17–20)

We hypothesize that *CYP2D6* genotype-guided prescribing results in greater reductions in pain severity and interference compared to a conventional prescribing approach in patients with cancer-associated pain. To test this hypothesis, we aim to determine the effect of prospective *CYP2D6* genotype-guided selection of opioid analgesics for cancer patients on pain and symptom severity and interference with daily living.

Methods

Study overview

Precision Medicine Guided Treatment for Cancer Pain is a pragmatic clinical trial being carried out at two independent cancer centers to determine the effect of *CYP2D6* genotype-guided selection of opioid therapy on cancer pain management. Patients are randomized to a genotype-guided or conventional approach to pain management, with patient reported pain-related outcomes (questionnaires) assessed at baseline (enrollment) and 2, 4, 6, and 8 weeks after enrollment (follow-up). The study design flow chart is shown in Figure 1.

Study population, location, and personnel

A total of 200 adult patients will be enrolled, with 100 enrolled at University of Florida (UF) Health Cancer Center in Gainesville, FL and 100 enrolled at Moffitt Cancer Center in Tampa, FL. UF Health Cancer Center is a nationally recognized academic cancer center with over 350 researchers and clinicians serving over 10,000 patients, annually, with sites in Gainesville, Jacksonville, and Orlando, FL. Moffitt Cancer Center and Research Institute is a National Cancer Institute (NCI)-designated Comprehensive Cancer Center located in Tampa, Florida. Moffitt collaborates with multiple health care systems across the state serving over 55,000 patients annually. The protocol was approved by the IRB at each institution.

Inclusion criteria for the study are age ≥ 18 years, diagnosis of histologically or cytologically proven solid tumor with metastasis, reported pain score of 4 or higher on a scale of 0–10 on

presentation to clinic, and receiving treatment at UF Health Cancer Center or Moffitt Cancer Center for outpatient management of cancer-associated pain. Patients who have undergone major surgery within the last three months or are scheduled to undergo surgery during the study period (8 weeks), have a documented psychiatric or neurological condition that would interfere with study participation, have had a liver transplant, or are allergic to opioids are excluded. Potential participants are identified at the time they present to clinic and are approached by a research team member about study participation.

The research team is composed of pharmacists with expertise in pharmacogenetics, physicians with expertise in cancer pain management, clinical pathologists, research coordinators, nurses, and statisticians. Team members at UF Health and Moffitt maintain bi-weekly telephone calls and email exchanges to consolidate data collection, discuss challenges, and ensure protocol adherence between the two sites.

Enrollment and randomization

Participants who provide informed consent are randomized in a 1:1 manner to receive *CYP2D6* genotype-guided (n=100) or conventional (n=100) selection of pain medication. The randomization schedule was developed in permuted blocks to maintain approximately equal numbers of patients in each group at any point throughout the study.⁽²¹⁾ Genotyping remains available clinically, and MDs are not prohibited from ordering a clinical *CYP2D6* test for patients in the conventional group. However, if a *CYP2D6* genotype order is placed for a patient in the conventional group, the patient is withdrawn from the study at that time point.

Intervention

At baseline, genetic samples are collected via buccal swab from patients in both arms. For the genotype-guided group, samples from both sites are sent to UF Health Pathology Laboratories for *CYP2D6* clinical genotyping. For the conventional pain management group (usual care), the sample is sent to the UF Center for Pharmacogenomics for *CYP2D6* genotyping for research purposes only at the conclusion of the study. Patients in both groups are asked to provide additional consent for the storage of their remaining sample and data for future research to identify additional genetic determinants of opioid response.

Patients in the conventional treatment group will continue to receive standard of care for their cancer related pain.⁽²⁾ For those randomized to the genotype-guided group, *CYP2D6* results are incorporated into their electronic health record (EHR). A pharmacogenomics pharmacist from the UF Health Personalized Medicine Program or Moffitt Cancer Center Personalized Medicine Clinical Service provides an interpretation of the genotype results and drug therapy recommendation via a consult note in the EHR. The consult note is also sent via email to the treating physician along with instructions on how to locate the results and recommendation in the EHR. For patients with PM, IM, or UM phenotype (based on genotype results), the pharmacist recommends avoiding oxycodone, hydrocodone, tramadol, and codeine, because of an increased risk for reduced analgesic response (in PMs or IMs) or toxicity (in UMs). Morphine, hydromorphone, fentanyl, or other analgesics without metabolic dependence on the *CYP2D6* pathway are recommended for these patients. A

sample consult note is displayed in Figure 2. For NMs, no change in opioid prescribing is recommended based on *CYP2D6* genotype. However, for NMs taking strong or moderate *CYP2D6* inhibitors (e.g. fluoxetine), which could phenotypically convert the phenotype to PM or IM, recommendations are also made to avoid opioids dependent on *CYP2D6*.⁽²²⁾ Changes in analgesic therapy are ultimately made at the discretion of the physician. A clinical decision chart to assist physicians with interpreting genotype results is also provided and displayed in Figure 3.

Questionnaires administered at baseline and at 2, 4, 6, and 8 weeks include the Brief Pain Inventory-Short Form (BPI-SF), M.D. Anderson Symptom Inventory (MDASI), assessment of previous 24-hr medication use, and additional questions related to quality of life (e.g. general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life).^(23–25) Additional data collected at baseline, via patient interview or EHR review, include the Pain Catastrophizing Scale (PCS); demographic information (e.g. age, sex, race, ethnicity); clinical data [e.g. date of cancer diagnosis, cancer type, disease stage, comorbidities, medications (including herbal supplements and nonprescription medications)]; types and dates of previous and current cancer treatment (e.g. surgery, chemotherapy, immunotherapy, or radiotherapy); and social data (e.g. education and income levels, caregiver status, use of alcohol and tobacco).⁽²⁶⁾ Opioid medication, opioid dose, and adjuvant medications are assessed via the EHR and verified in person or by telephone at baseline and with each follow-up. Any change in opioid therapy (change in dose or drug) is captured in the drug log on the follow-up questionnaires and through EHR review when the patient completes the study. Because physicians and patients are not obligated to follow the genotype-guided recommendations from the pharmacist, adherence to recommendations is also monitored by the study team to assess the feasibility and acceptability of genotype-guided therapy.

On average, completing the consent process and baseline questionnaires and interview takes approximately 30 minutes, while questionnaires at each follow-up take about 10 minutes to complete. The 2, 4, 6, and 8 week questionnaires may be completed at regularly scheduled follow-up visits (if patient is returning for regular care), by telephone with a member of the research team, or through an online link. Alternatively, blank follow-up forms may be provided to the patient with the dates prefilled for the patient to complete at his or her convenience on those dates. Completed questionnaires are submitted to investigators via direct electronic patient input, US mail, fax, e-mail, or manually collected by a research team member. The research coordinator makes up to 3 attempts to contact the patient for a reminder to complete questionnaires at each follow-up point.

Genetic testing

Clinical *CYP2D6* genotyping for the genotype-guided arm is conducted in the UF Health Pathology Laboratories, accredited by the College of American Pathologists (CAP) and certified through Clinical Laboratory Improvement Amendments (CLIA), using a Luminex® 100/200™ System (Luminex; Austin, TX) and xTAG® *CYP2D6* Kit v3 Assay. This genotyping platform detects *CYP2D6**2, *3, *4, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41 alleles, *5 (gene deletion), and gene duplication. Genotypes are translated into the

PM, IM, NM, or UM phenotype, using activity score per CPIC recommendations, with results placed in the EHR within 2 weeks.(11, 27) Genotyping for *CYP2D6* variants for the conventional arm will be performed at the end of the study at the UF Center for Pharmacogenomics using a protocol previously described.(28, 29)

Data analysis

The aims of the study are to determine the feasibility and effect of the *CYP2D6* genotype-guided selection of opioid management in cancer-associated pain. Feasibility will be evaluated through patient acceptance of genetic testing, genotyping turn-around time, and physician acceptance of genotype-guided recommendations. The primary endpoint is differential change in pain severity by treatment strategy (genotype-guided versus conventional pain management). Secondary endpoints include change in pain and symptom interference with daily living and adverse drug effects. The endpoints are assessed by the BPI-SF and MDASI questionnaires.

Sample size was based on determining differences in BPI-SF pain scores between groups. A total of 100 patients in each group will provide over 80% power with an alpha of 0.05 to detect a 1 point change in pain severity on the BPI-SF interference scale (reported with final follow-up), assuming a standard deviation of 2. This is a reasonable benchmark consistent with IMMPACT recommendations for studies designed to identify minimal clinically important changes of pain in clinical trials.(30)

Results

A total of 74 patients have been approached for participation in the study. Of these, 65% (48/74) enrolled. The most common reason stated for not participating was related to the questionnaires being too time consuming. Of the 48 patients enrolled (25 at UF and 23 at Moffitt), 21 were randomized to the genotype-guided group and 27 to the conventional treatment group. Among all patients, the mean pain score was 5.2 ± 2.0 , and 85% were taking oxycodone at baseline. Of the 48 patients enrolled to date, 94% (45/48) have completed the baseline questionnaire, and 58% (28/48) have completed at least one follow-up questionnaire.

The median time until genotype result was reported in the EHR was 9 (IQR, 7–12) days. Based on genotype result, 4 patients were classified as IMs, and the rest were classified as NMs. Of the NMs, two were taking a moderate *CYP2D6* inhibitor that resulted in phenotype conversion from NM to IM.(11) We reviewed physician responses for patients with any genotype that resulted in a recommendation for a change in therapy. This included 6 patients with the IM phenotype identified to date. For one of these patients, a change in opioid therapy was made and was consistent with genotype-guided recommendations. For an additional patient with the IM phenotype, the physician noted in the electronic health record that he had a low threshold for switching opioids if pain continued or worsened, but did not make any drug change during the study period. The other 4 patients with IM phenotype did not have any changes in therapy during the study period.

Initially, the study was designed to follow each patient for a 4-week duration, with questionnaires completed each week. However, it became clear after the first few patients were enrolled that it was necessary to allow two weeks for the return of genotype results for this multi-institutional pragmatic study. Thus, the design was revised to allow 8 weeks of follow-up, with questionnaires completed every 2 weeks to ensure that adequate time for genotype results, treatment recommendations, and implementation were allowed.

The following case outlines the clinical flow for a patient randomized to the genotype-guided arm and found to have the IM phenotype, warranting a clinical recommendation to avoid opioids dependent upon CYP2D6 metabolism. A female, 35 years of age, diagnosed with colon cancer with metastasis to the liver was taking oxycodone ER 30 mg twice daily (60 mg/day) and oxycodone 5 mg every 4–6 hours for breakthrough pain (30 mg/day). She reported a score of 6 out of 10 on a pain scale to the triage nurse at the time she presented to a regularly scheduled outpatient visit to the primary oncologist. She was subsequently approached by the study coordinator while she was waiting to meet her physician and agreed to study participation. After obtaining written, informed consent, a buccal swab sample was collected for genotyping, and the patient completed the baseline questionnaires. She was randomized to the genotype-guided treatment group, and her *CYP2D6* genotype returned as **3/*41*, corresponding to the IM phenotype. The genotype result was entered into the EHR on day 9, along with an accompanying consult note by the clinical pharmacist providing a recommendation to change opioid therapy to morphine, hydromorphone, fentanyl, or another analgesic without dependence on the CYP2D6 pathway. The patient returned for a scheduled clinic visit 22 days after enrollment (13 days after genotype return), at which time, the physician changed her oxycodone ER to transdermal fentanyl 50 mcg/hr, which has an equianalgesic effect of 60 mg of oxycodone per day, and increased the dose of short acting oxycodone to 10 mg every 4 hours for breakthrough pain.(2) The patient filled the fentanyl prescription 7 days later, after receiving prior authorization for the medication from her insurance, and started the new pain regimen at day 29 (20 days after genotype return). The patient completed follow-up questionnaires at 1, 2, 3, and 4 weeks after enrollment (prior to the protocol change to allow follow-up questionnaires at 2, 4, 6, and 8 weeks). As shown in Figure 4, her “worst”, “average”, and “least” pain scores all decreased by day 30 (week 4) compared to her baseline measurements.

Discussion

A multi-disciplinary team including pharmacists, oncologists, supportive care physicians, nurses, clinical pathologists, clinic coordinators, and biostatisticians was involved in designing the study, which included selecting patient eligibility criteria, mapping logistics of patient recruitment, identifying assessment tools, establishing strategies for communication between the research staff and physicians, administering questionnaires for data collection, and developing the statistical analysis plan.

Our population includes patients with any solid tumor with metastasis which, based on patient census at each site, allows for the greatest number of eligible participants, while maintaining a common factor of “painful disease burden”. Selecting a pain score of 4 or higher as the threshold for intervention in this population was based on the NCCN

guidelines for Adult Cancer Pain, in which a pain score of 4–6 indicates moderate pain, and a score of 7–10 indicates severe pain, both of which warrant addressing the patient's pain at that clinic visit, including but not limited to titrating short-acting opioids.(2)

After enrolling the first 5 patients, it was realized that a one-week turn around for *CYP2D6* genotype results, as initially planned, was not clinically feasible. This required a revision in the protocol from assessing pain-related outcomes at 2, 3, and 4 weeks to assessing them at 2, 4, 6, and 8 weeks. This revision allows more time for 1) the return of *CYP2D6* genotype results in the EHR; 2) review of results by the treating physician; 3) physician follow-up and discussion of results with the patient; 4) change in opioid prescription if warranted; and 5) assessment of the effects of any drug change on patient-reported pain. Multiple follow-ups also enable us to identify, for future research, the endpoint wherein individual variability is balanced and treatment effects are maximized.

The greatest clinical value of pharmacogenetics may be to have the information available at the time of initial opioid prescribing to minimize the trial and error needed to find the most effective pain medication. This is illustrated with the patient case presented, in which the patient was receiving inadequate pain relief from oxycodone, reporting pain scores of 4 to 6 out of 10, possibly as a result of her IM phenotype and inability to fully activate oxycodone to oxymorphone. Once her therapy was switched to an equianalgesic dose of fentanyl, which is not dependent on *CYP2D6* for metabolism, she reported improved pain relief, with an average pain score of 2/10. Had genotype been available at the start of her therapy, she could have perhaps avoided a prolonged period with inadequate pain control.

To date, most patients in our study were taking oxycodone at the time of enrollment, in line with prescribing practices at our institutions. Eleven percent of the oxycodone dose is metabolized by *CYP2D6* to oxymorphone, which has 40-fold higher affinity for the μ -opioid receptor.(31, 32) Lower oxymorphone concentrations have been reported in *CYP2D6* PMs and IMs compared to NMs following a single dose of oxycodone, and while the data are not entirely consistent, there is evidence that lower oxymorphone concentrations in PMs results in lesser analgesia and more opioid consumption.(18–20, 33) In determining recommendations for patients taking oxycodone or other opioids metabolized by *CYP2D6*, our team adapted language from the CPIC Guidelines for *CYP2D6* genotype and codeine therapy. (11) While the guidelines focus on codeine, for which there are the most data on genotype associations with response, they recommend use of an alternative analgesic other than oxycodone or other *CYP2D6* substrates for *CYP2D6* PMs and UMs. This was the basis for our recommendation to avoid oxycodone (and other opioids dependent on *CYP2D6* metabolism) for PMs and UMs. For IMs, the guidelines recommend using label-recommended codeine dosing and considering a switch to an alternative analgesic if no response. (11) Because of the uncertainty of response in IMs, the high pain burden in cancer, and some data reporting lower oxymorphone concentrations with the IM phenotype, we chose a more proactive approach for IMs. Therefore, similar to PMs and UMs, we recommend a change to an opioid not metabolized by *CYP2D6*. In the patient case presented, this approach led to improved pain control.

Developing the process for reporting genotype results to the physician as part of the study was primarily influenced by physician preference. Practitioners requested that, in addition to the research note loaded into the EHR, an email containing the recommendation be sent directly to them. Without clinical decision support integrated into our EHR for this implementation, this additional step was felt to be necessary to alert the physician of the genotype result. However, pending results of the current trial, future strides may be made to build clinical decision support into the EHR to facilitate interpretation and translation of genotype results into opioid prescribing decisions or a prompting to obtain genotyping if not already available in the EHR at the time of initial narcotic prescribing.

To ensure that the protocols at both sites are carried out in a similar fashion, we decided to work with a limited number of practitioners who stated interest in integrating *CYP2D6* genotype into prescribing decisions. Clinic coordinators work directly with nursing staff to identify eligible patients who present to their regularly scheduled outpatient clinic appointment and report pain upon evaluation. Both sites have designated coordinators who initiate and maintain all patient engagement and interaction. When possible, to build a rapport with participants and limit loss to follow-up, the same member of the research team who recruited the patient will maintain contact every 2 weeks with reminders to complete each follow-up questionnaire. Our follow-up engagement to date has relied on telephone calls and emails. Moving forward, in an attempt to improve questionnaire completion, we are meeting patients at their regularly scheduled clinic visits to request questionnaire completion at that time. Also, each site has a designated pharmacist who writes the clinical research recommendation using a common template between sites in an effort to maintain consistency between institutions and provide recommendations in a consistent and familiar format to the provider to facilitate interpretation.

We recognize some limitations to our study. First, patients are not blinded to their group assignment, which may introduce confounding. To help control for this, we plan to compare changes in pain scores between patients with a genotype that would lead to a recommendation to change therapy (e.g. PMs, IMs, and UMs) and those without (i.e. NMs). If the genotype-guided approach to pain management is successful, we would expect a change in pain intensity for patients with the PM, IM, and UM phenotype and no change for NMs. Secondly, the impact of a recommendation can only be evaluated if it is acted on and our initial data show that this happens the minority of the time. To improve adherence to genotype-guided recommendations, we are discussing adding electronic clinical decision support tools to alert physicians to patients with the *CYP2D6* PM, IM, or UM phenotype at the time an opioid that undergoes *CYP2D6* metabolism is prescribed, similar to that done for one of our previous implementations (34). As this is a pragmatic trial, with the ultimate prescribing decisions left to the discretion of the physician, we also will survey physicians at the end of the trial to assess their perception of the usefulness of having genotype results on prescribing decisions. We will specifically ask physicians if they followed genotype-guided recommendations, and if not, why not. This information will be used to inform future trials and broader pharmacogenomic implementation.

Conclusion

In summary, supportive care is recognized as an important component of care throughout cancer treatment, and improved pain and symptom management has been associated with decreased morbidity and mortality.(3, 25) An effective and efficient pain management strategy in patients with cancer may reduce the time needed to achieve adequate analgesia while limiting adverse effects. While previous studies have used retrospective and cross-sectional designs to assess the role of *CYP2D6* genotype in opioid selection, this trial “Precision Medicine Guided Treatment for Cancer Pain” is unique in that it will provide prospective data on pain-related outcomes with clinical implementation of genotype-guided pain management in a real-world setting. If this intervention proves to be beneficial, it could significantly improve pain management and limit adverse drug effects which are common issues with this class of drugs. Pharmacokinetic (e.g. choice of short-acting vs. long acting formulations) and pharmacodynamic (e.g. opioid binding affinity and receptor involvement) principles are commonly taken into consideration when selecting the best opioid therapy for pain management. Because pharmacogenomics is integrated into both of these clinical aspects, genotyping may also serve as an additional tool in selecting optimal therapy for an individual with cancer pain.

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Figure 1.
Study design flow chart. BPI-SF: Brief Pain Inventory-Short Form; MDASI: MD Anderson Symptom Inventory; EMR: Electronic Medical Record

CYP2D6 Pharmacogenetics Consultation UF Health Personalized Medicine Program

HPI:

Your patient (MRN xxxxx), is currently enrolled in the research study, Precision Medicine Guided Treatment for Cancer Pain (IRB xxxxx). This patient provided written consent on xx/xx/xxxx and was randomized to the genotype-guided group.

Relevant pain medication history:

Oxycodone ER 30 mg twice daily
Oxycodone 5 mg every 4-6 hrs for breakthrough pain

Drug allergies:

Doxycycline: Hives
Dicyclomine: Rash

Pharmacogenetic test results (xx/xx/xxxx):

CYP2D6 *3/41* **Intermediate Metabolizer (IM)** phenotype; decreased CYP2D6 enzyme activity)

CYP2D6 interacting drugs (as of xx/xx/xxxx):

None

Interpretation:

Oxycodone, tramadol, hydrocodone, and codeine are converted to more potent metabolites by the CYP2D6 enzyme. Intermediate metabolizers have decreased active enzyme and decreased metabolism of oxycodone, tramadol, hydrocodone, or codeine to their more potent metabolites. This patient's CYP2D6 genotype is associated with decreased production of oxymorphone, the more potent metabolite of oxycodone. Therefore, **this patient may have insufficient pain relief from oxycodone.**

Recommendations:

Oxycodone is **NOT RECOMMENDED** because this patient is predicted to be an **INTERMEDIATE METABOLIZER** of oxycodone based on CYP2D6 genotype. Consider alternative analgesics such as morphine, hydromorphone, or another analgesic not dependent on CYP2D6 metabolism.

For questions regarding this recommendation, please contact the UF Health Personalized Medicine Program:

Figure 2.

Example of a consult note based on *CYP2D6* genotype which is uploaded into the patients EMR.

Figure 3.
Quick-reference clinical decision tool to assist physicians in interpreting genotype results.

Figure 4. Timeline of self-reported pain scores by a patient with the IM phenotype, randomized to the genotype-guided arm.