Utility of Pharmacogenomic Testing and Postoperative Dental Pain Outcomes

Principal Investigator – Yanfang, Ren, D.D.S., MPH., PhD. Urgent Care/General Dentistry Department, Eastman Institute for Oral Health
Co-Principal Investigator/Monitor: Malmström, Hans, D.D.S. General Dentistry Department, Eastman Institute for Oral Health.
Sub- Investigator: Uribe Rivera, Armando, D.D.S. (OMS) General Dentistry Department, Eastman Institute for Oral Health

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Background

Opioid analgesics are the most common postoperative pain medications used among dentists in the United States.[1, 2] Although these medications are highly effective in the postoperative dental pain management, not all patients optimally benefit from this therapy. Many suffer adverse consequences such as nausea, emesis, and psychomotor impairment, and there is a high prevalence of opioid prescription misuse among substance abusers within the dental patient population.[3] Furthermore, the increase in annual opioid-related deaths continues to rise, impacting public health and leading clinicians and dentists to develop new strategies to reduce opioid prescription, while at the same time maintaining pain control outcomes. [4, 5] The use of non-opioid analgesics including ibuprofen and acetaminophen in the management of postoperative dental pain has demonstrated equivalent or superior analgesic effects compared to opioid analgesic therapies, typically with significantly less adverse effects. [6, 7] However, despite these results, dentists have encountered a high variability in the success of non-opioid analgesic responses among the postoperative dental pain population. This has led many to continue use of opioid analgesics as first-analgesic-line therapy in order to assure adequate analgesia and a positive postoperative recovery.[8] As such, the combined formulation with hydrocodone and acetaminophen (i.e. Vicodin®) remains the analgesic most prescribed by dentists for controlling postoperative dental pain in the U.S. [9]

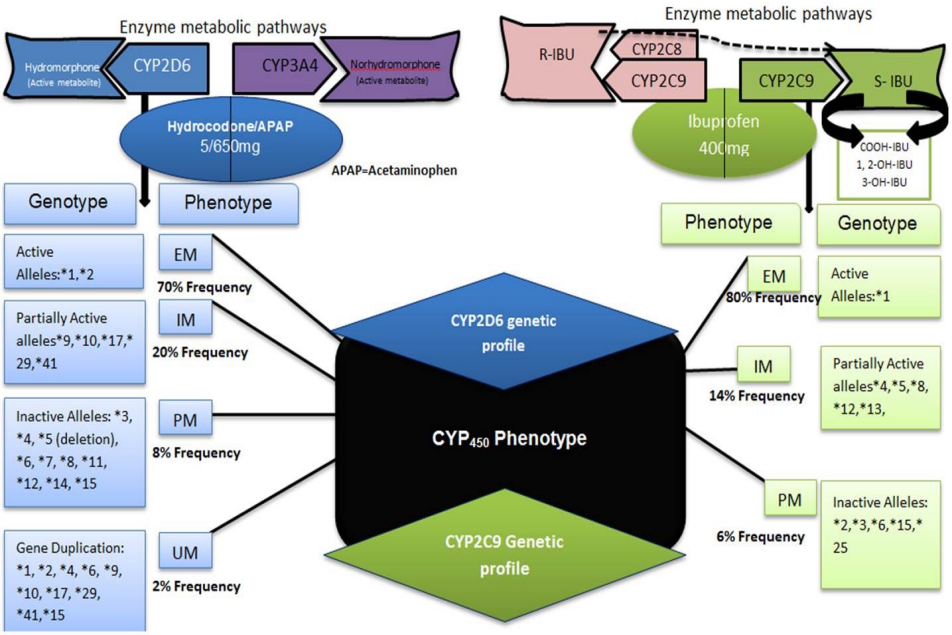


Figure 1. Representative for both cytochrome P450 superfamilies including; CYP2D6 and CYP2C9 enzyme genes. Medications administered in this proposal will include; (1) Hydrocodone/acetaminophen 5/650mg (blue) (2) Ibuprofen 400mg (green) and acetaminophen 650mg (not shown in this figure)

To date, the use of pharmacogenomic methods in medicine has broadened our understanding of the important role of genes and different phenotypes/genotypes that make each individual unique in pain responses, including drug biotransformation, transportation, and drug-related side effects to name a few.[10, 11] For example, ibuprofen (IBU) is a racemic

mixture of two enantiomers, the pharmacologically active S-IBU and the virtually inactive form, R-IBU. However, an estimated 50-65% of R-IBU undergoes inversion to the active S-enantiomer.[15] Inversion of R-IBU to S-IBU occurs via an acyl-CoA thio-ester by the enzyme Alpha-methylacyl-coenzyme A racemase (AMACR) (Figure 1; dashed arrow). [16] This can occur pre-systemically in the gut [15] as well as in the liver. [17, 18] The primary metabolism (deactivation/facilitated excretion in this case) of racemic ibuprofen is an oxidative process and involves primarily membrane-associated cytochrome P450 (CYP) enzymes CYP2C9 (S-IBU and R-IBU) and CYP2C8 (R-IBU) (Figure 1).[12,13,14] The major primary metabolites found in the urine including one carboxy-IBU and three hydroxyl metabolites; 2-OH IBU; 3-OH IBU and 1-OH IBU (a minor product). These metabolites do not have apparent pharmacological activity in the system. [15] Secondary metabolism of IBU also occurs by glucuronidation via the UGTs pathway [19] (not shown in figure 1). Previous studies have shown that individuals with variant alleles producing inactive forms of these CYP have very low clearance rates compared with non-carriers of mutations (Garcia et al., 2004). While this may help prolong the analgesic effect of IBU, it also has been shown to result in increased risk for gastrointestinal bleeding and other adverse effects (Blanco et al., 2008; Pilotto et al., 2007; Carbonell et al., 2010). The frequency of distribution among the population for CYP2C9 (the major gene-pathway studied in this clinical trial) phenotype/genotypes is 80% Extensive Metabolizers [(EM) normal medication response], 12% Intermediate Metabolizers [(IM) abnormal medication response] and 8% PM Poor Metabolizers [(PM) abnormal medication response](Figure 1; green color). Given the equivalence/superiority of IBU over standard opioid therapies, we posit that individuals with normal CYP 2C9 (no genomic variation; approximately 80% of the population) will respond favorably to the administration of IBU for management of postoperative dental pain, while those with abnormality of CYP2C9 (approximately 20% of the population) will be more appropriately treated using alternative agents (i.e. opioids; acetaminophen).

The second cytochrome P450 of relevance to this proposal is CYP2D6, which is an enzyme critical for the metabolism of numerous opioids. Unlike inactivation/elimination functions described above for CYP2C9, the efficacy of certain opioid compounds (such as hydrocodone) is dependent upon successful metabolic conversion by CYP2D6 from the inactive pro-drug form to an active metabolite. The frequency of distribution among the population for CYP2D6 phenotype/genotypes is (Figure 1; blue color): 70% [Extensive Metabolizers (EM); normal medication response], 20% [Intermediate Metabolizers (IM); abnormal medication response], 8% [Poor Metabolizers (PM); abnormal medication response] and 2% Ultrarapid Metabolizers [(UM) abnormal medication response]. Studies have demonstrated that ultrarapid CYP2D6 metabolizers experience increased analgesic effects from oxycodone (due to rapid conversion prodrug to an active form), but have increased side effects such as nausea and vomiting (Samer et al., 2010). Conversely, poor metabolizers experienced a significant reduction in analgesic efficacy due to the slow conversion to the active drug. We posit that individuals with abnormal CYP2C9 function (ibuprofen inappropriate), but normal CYP2D6 function (normal response to opioid prodrugs), will benefit from the administration of hydrocodone for the management of postoperative dental pain.

We further posit that individuals with both abnormal CYP2C9 and CYP2D6 function, will benefit from the administration of acetaminophen for the management of postoperative dental pain. Acetaminophen is biotransformed by CYP2E pathway (not shown in Figure 1), and its use does not overlap with any of the other drugs' metabolic enzyme pathways. Determination of CYP2E status is currently unavailable, so assignment to this medication is by default.

Summarizing the discussion above, we suggest that we can minimize the prescription of opioid analgesics by at least 80% in the acute postoperative dental pain population. Therefore, *we postulate that the integration of a pharmacogenomic testing to guide the prescription of ibuprofen and acetaminophen could lead to improved clinical postoperative dental pain outcomes and significantly reduce prescribing of opioid analgesics by dentists.*

This hypothesis will be addressed with the following Specific Aims:
Specific aim 1: To compare the pain control outcomes between a single-dose of pharmacogenomics-testing-driven-prescription of ibuprofen (400mg) or acetaminophen (650mg) with those of single-dose (standard of care) of combined formulation of hydrocodone and acetaminophen (Norco®; 5/650mg).

Specific aim 2: To determine the number of patients who did not require prescribed opioid analgesic 'rescue' after pharmacogenomic-guided acute postoperative dental pain management versus those taking the non-guided combined formulation of hydrocodone and acetaminophen.

We will achieve these aims through a double-blind-randomized clinical trial of healthy adults, who have undergone extraction of at least three impacted mandibular third molars (wisdom teeth). Subjects will be randomly assigned to one of two groups: 1) Experimental – will receive a single dose of pharmacogenomics testing-driven-prescription of ibuprofen (400mg) (for those, whose genetic testing suggests they will respond normally to ibuprofen); or acetaminophen (650mg) (for those, whose genetic testing suggests they will respond abnormally to ibuprofen); and 2) Control - will receive a single dose of standard of care medication for pain associated with the extraction of impacted third molars, Norco® (hydrocodone/acetaminophen; 5/650mg). All subjects will receive preoperative pharmacogenomics testing through saliva sample collection (for phenotype recognition and genotype analysis) by pharmacogenomics test kit (PGxOne®;Admera HealthTM; N.J). We will focus on assessment of the short-term pain outcome using a single dose of medication that potentially impacts the long-term use and prescription of opioids in the management of postoperative dental pain following the extraction of impacted third molars.

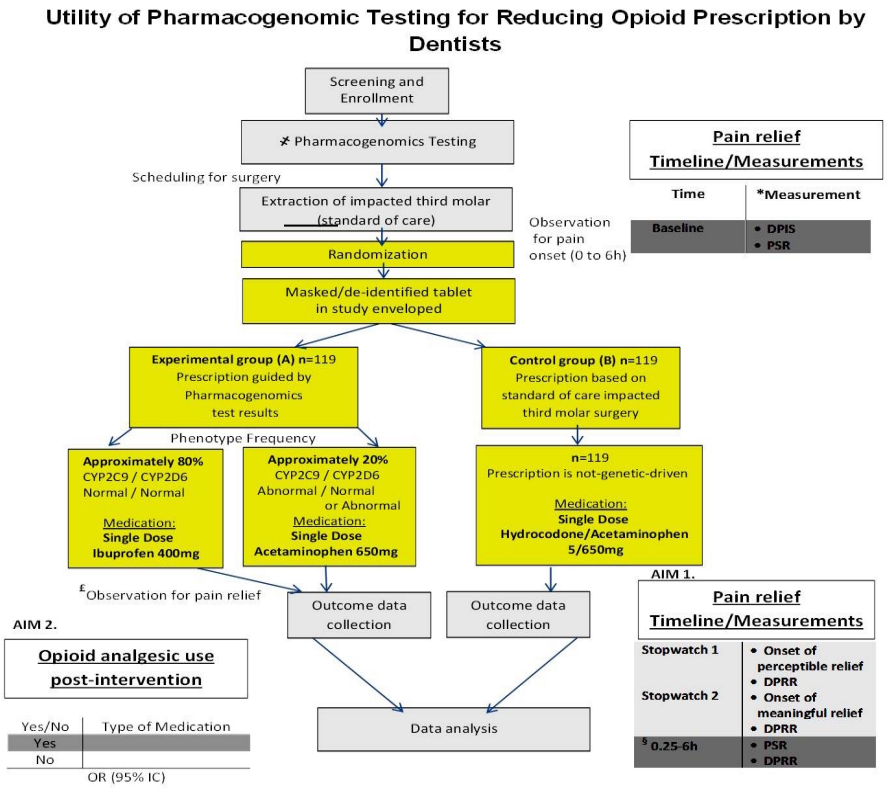
1.2 **Purpose.**

To determine whether pharmacogenomic testing can help dental practitioners select appropriate non-opioid pain medications including ibuprofen and acetaminophen in the management of postoperative dental pain and whether data from this testing has an effect on both increased pain outcomes and reducing opioid prescription pattern by dentists.

2. STUDY DESIGN

2.1. **Overview (figure 2)**

A randomized and double-blind clinical trial will be fashioned to determine the clinical utility of pharmacogenomics testing to guide the prescription of non-opioid analgesics including; 1) ibuprofen (400mg). We will use postoperative dental pain related



⊀ Phenotype results will be delivered immediately based on pharmacogenomics test results report included in pharmacogenomics test kit. Genotype results will be delivered later in a 3-week-period.
* Definition. **DPIS,** dental pain intensity scale. **PSR,** pain severity rating scale. **DPRR,** dental pain relief rating.
§ Measurement times will include baseline, 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 3h, 4h, 5h and 6h.
£ If pain relief is not accomplished by first-line-analgesic therapy, then rescue medication will be administered as follows: **Experimental group:** Oxycodone/acetaminophen (5/325mg). **Control group:** Based on pharmacogenomics test results.

Figure 2. Representative flowchart of activities on study

to impacted third molar extraction, as study model. Both screening for eligibility and informed consent will occur at the preoperative appointment. All study participants will receive a preoperative pharmacogenomic testing through saliva collection (≥5mL). Following impacted third molar surgical removal, those who meet final eligibility criteria will be assigned (by computer-generator-randomization) to 1 of 2 treatment groups include experimental (A) and control (B) groups. Pain medications and pharmacogenomic results will be blinded for both the investigators and participants (see section 7.4). Pain medication tablets will be provided into blister cards, envelops or containers to a non-blinded research collaborator by the investigational drug department at URMC. Of note, the the investigational drug department will identify the subject's genetic profile related to the response to pain medication based on the results sent by genetics laboratory. . Individuals in the experimental group will receive the pharmacogenomics test driven-prescription of ibuprofen (400mg; 2 tablets of 200mg), or acetaminophen (650mg; 2 tablets of 325mg), based on (genetic profile) phenotypic (normal or abnormal metabolic enzyme rate biotransformation) results delivered by the pharmacogenomic testing. Subjects in the control group (B) will receive the standard of care for extraction of impacted third molar postoperative pain with hydrocodone/acetaminophen (Norco®5/650mg; 2 tablets of 2.5/325mg). All medications in this clinical trial will be administered as a single dose PO Final evaluation of eligibility will be based on achieving a minimum level of postoperative pain of at least 50mm out of a possible 100mm by the visual analog-Dental Pain Intensity Scale (DPIS) within 6 hours after surgery. If applicable, patients who fall asleep post-intervention during the final determination of eligibility, will be awakened as necessary to complete the DPIS.
All study data including pharmacogenomic test results, study times, pain control measurements, type of pain medication used among others will be recorded on the case report forms (CRFs)..

2.2. **Rationale for Study Design**

This study design follows the standard for clinical pain trials. The use of pharmacogenomics testing in this study is intended to effectively guide the prescription of ibuprofen and acetaminophen, reducing the need for opioid analgesics in the management of impacted third molar postoperative pain.

2.3. **Rationale for Dosage**

Pain management therapies using ibuprofen, acetaminophen and narcotics in this study follow current standard-of-care recommendations and guidelines for postoperative dental pain (Hersh et al., 2011). These drug/dose recommendations, based on severity of pain, are illustrated in Figure 3, and include updated recommendations for the use of acetaminophen for moderate pain (Qi et al., 2012).

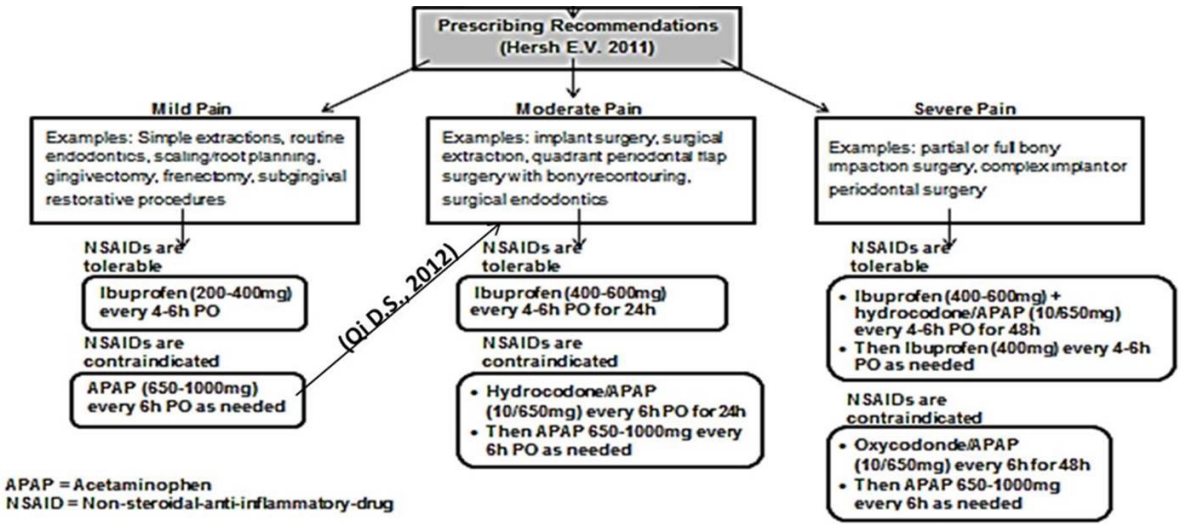


Figure 3. Current standard-of-care prescribing recommendations for postoperative dental pain management. Daily ibuprofen doses for acute postoperative dental pain should not exceed 2400mg. Daily APAP doses should not exceed 4000mg. Short-term use of NSAIDs are Contraindicated in patients with history of gastrointestinal ulceration and aspirin intolerance/ Cross-sensitivity (eg, aspirin- or NSAID – induced allergy or asthmatic attacks) or patients receiving anticoagulation therapy. (Hersh *et al* 2011). It is important to note that acetaminophen (APAP) 650-1000mg is now also effectively administered for moderate-severe postoperative dental pain (Qi D.S. *et al* 2012)

CHARACTERISTICS OF THE RESEARCH POPULATION

2.4. Subject Characteristics

a) **Number of Subjects:**
A total sample size of 238 individuals will be enrolled. 119 subjects will be assigned in each of the treatment groups.

b) **Gender and Age of Subjects:** Equitable inclusion of both men and women will be undertaken in this study. The participation of healthy adult subjects will be encouraged in this study. Those individuals aged 18 to 35 years will be invited to participate in this clinical trial.

c) **Racial and Ethnic Origin:** Ethnic distribution will be equitable in this research study. Furthermore, this study does not have any enrollment restriction based upon race or ethnic origin.

d) **Vulnerable Subjects:** Not applicable for this study.

2.5. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:**

1) ASA I or II

2) Age 18-35 years

3) Patients scheduled to undergo surgical removal of 1 or more impacted third molars, at least 1 of which must be a bony mandibular impaction.

4) Patients who are able to read, comprehend, and sign the consent form, and willing to stay in the study unit for up to 12 hours.

5) Patients who are reliable, cooperative, and of adequate intelligence to record the requested information on the questionnaire form(s).

6) Women of childbearing potential who are not pregnant, as assessed by a urine pregnancy quick test on the day of the procedure, prior to surgery. Women must be using a method of birth control deemed acceptable by the investigator and continue to use this method during the duration of dosing with study medication

7) Patient who develop sufficient levels of pain (rated at 50mm or more out of a 100 mm) on the DPIS within 6 hours post-surgical extraction.

8) Patients who agree not to take analgesics other than protocol-defined rescue analgesics during the post-operative treatment period of 6 hours.

9) Patients who agree to refrain from alcohol and sedative consumption during the post-operative period of 6 hours.

b) **Exclusion Criteria:**

Subjects with:

1)Known opioids and NSAIDs allergies (or induced asthmatic attacks)
2)Known history of opioid abuse
3)Recent history of gastrointestinal ulceration
4)History of aspirin intolerance/cross-sensitivity
5)Recent myocardial disease
6)Uncontrolled hypertension
7)Patients receiving anticoagulation therapy
8)Uncontrolled diabetes
9) Pregnant women
10)Immunosuppression
11)Recent history of opioid or NSAID therapies
12)Subjects who do not achieve a qualifying baseline pain threshold of 50mm out of 100mm on the visual analog DIPS within 6 hours of completion of surgery

2.6. **Discussion of Subject Population**

The above inclusion/exclusion criterion for this study is selected based on minimizing the risks and enhancing subject's safety. This study is designed to determine the clinical use of a pharmacogenomics test to guide the prescription of non-opioid analgesics in the management of impacted third molar postoperative pain. Those subjects with the above medical conditions within the exclusion criteria may be compromised by the use of any of the pain medications, thus they are excluded for safety issues.

3. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

3.1. Method of Subject Identification And Recruitment

Recruitment process.
Patients will be approached by a research assistant (see also section 7.3) at the time of their preoperative evaluation and will be invited to enroll in the study. Those who are interested in participating in our research, after informed consent, will be screened to determine eligibility prior to enrollment based on inclusion/exclusion criteria. Patients scheduled to undergo surgical removal of 1 or more impacted third molars, at least 1 of which must be a bony mandibular impaction.

Final screening determination.
Final screening evaluation will be completed following surgery (baseline), those patients who achieve a minimum level at least 50mm out of a possible 100mm of postoperative pain utilizing the visual analog-Dental Pain Intensity Scale (DPIS) will be enrolled. DPIS is a standard of practice dental pain assessment used in clinical trials in dentistry. This measurement is based on a scale of 0-100mm. Patients who fall asleep while in the clinic during final determination of the eligibility stage will be awakened by study personnel as necessary (i.e. hourly) to administer the DPIS.

Subject's Privacy statement
The identification of subjects will be protected. The investigators and research personnel will make every effort to protect the subject's privacy in addition to avoiding undue influence. Only investigators with routine access to prospective subjects (or subject records) will approach and recruit those individuals directly ("routine access" meaning the investigator already has a clinical/academic reason to know/review a patient's record or is known to the prospective subject). Investigators who will not have routine access to prospective subjects will not contact subjects directly (i.e., no "cold calls"); they will work through the individual(s) with routine access. Subject's Private information including medical records in this study will not be made public.

3.2. Process of Consent

Written informed consent, in accordance with local clinical investigation regulations at the University of Rochester will be obtained prior to participation in the study. The study investigator or research coordinator will provide a description of study protocol (including any potential and possible hazards) and procedures. Information will be given in oral and written form. The patient information provided will be in a language understandable to the patient, and will not include any language that appears to waive any of the patient's legal rights, or appears to release the Investigator or Institution from liability or negligence. In addition, the consent form includes HIPPA language, which explains to the patient how personal information will be managed and protected. Investigators will inform all subjects taking part of this study that potential treatments for postoperative dental pain management include; 1) Tylenol, Ibuprofen or a narcotic such as hydrocodone/acetaminophen or oxycodone/acetaminophen (rescue medication).

The investigator will provide the prospective patient sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence, and will discuss any questions the patients may have. The Investigator will explain to the patient that withdrawal from the study is possible at any time without detriment to care. The Investigator will then ask the patient to give consent in writing.

The consent will include acknowledgement that medical records and medical data derived from study may be forwarded to the responsible authorities or federal authorities.

4. METHODS AND STUDY PROCEDURES

Standard of care procedures.

Impacted third molar surgical removal.

Patients will report to the clinic on the morning of their surgery and will have fasted after midnight, except for clear liquids up to 2 hours prior to surgery. At the surgeon's discretion, oral fluids prior to surgery will be allowed. The third molar surgical removal will be performed under standard of care protocols. Once local anesthesia is achieved, impacted third molar removal will be undertaken through full-thickness mucoperiosteal elevation flap, surgical bone removal [to uncover dental structure (if applicable)] with or without dental section (at surgeon's discretion). Simple stiches or continuous stiches with resorbable suture materials will be utilized to close surgical incisions. Patient's vital signs will be monitored all the time during surgery.

*Ice Pack use for postoperative pain management adjuvant treatmen*t.

The use of ice packs to the affected surgical site of the face and jaw will be permitted in this study. However the use of ice packs will be allowed 2 hours after dosing with pain medication. (See details in section 5).

Research procedures

DNA collection

DNA from all subjects who participate in the clinical trial will be collected by saliva samples. Saliva specimens will be stored into de-identified Eppendorf tubes and will be sent to Admera Health laboratories (S. Plainfield, N.J.), under standardized protocols to handle DNA sampling, for DNA sequencing. The analysis of these samples will provide the phenotype and genotype data (CYP2C9; CYP2D6) to categorize patients accordingly to normal or abnormal genetic profile related to the response of pain medications involving hydrocodone and ibuprofen. Laboratory analysis will include PCR with amplified methods in addition to next generation DNA sequencing technology.

Baseline

For the purpose of this study baseline is defined as the time following the procedure when the subjects are asked to rest quietly in the dental chair before pain medication is administered. At baseline the patients will not be allowed to wear a watch and the room will not have a clock. Patients will be supplied with 2 stopwatches that will have the time display covered when in use. The patients will complete the Baseline pain threshold (at least 50mm out of possible 100mm-VAS). Those subjects who do not achieve a qualifying baseline pain threshold at 6 hours of completion of surgery will not continue in the study.

Extended postoperative stay at clinic facilities

Subjects who meet inclusion criteria will be informed by written consent and by word (from Investigator or research coordinator) that he/she will stay for up to 12 hours after intervention. We will measure pain after local anesthesia effect wears off the individual in around 4-6h after procedure. We will start the pain therapy described in figure 2 and the patient will stay at the dental clinic until a meaningful pain relief is achieved. This may take from 2-6 hours after administration of pain medication, depending on each individual. During this time we will monitor the subject's vital signs and pain symptoms. During the stay in the dental clinic for pain assessment, subjects will be provided with dietary supplements appropriate for the immediate postoperative stage that include, cold foods (water, clear fruit juices, ice-cream, , etc.)

Pharmacogenomics test. **(PGxOne®, Admera Health, N.J. U.S.A)**

The pharmacogenomics test includes a kit with two laboratory tubes or containers. 1 special laboratory tube is used for saliva collection and the second laboratory tube contain the buffer solution to stabilize the cells and DNA from the body fluid. (PGxone™ [Admera Health, N.J, U.S.A])Results will be delivered 7-10days after sending the saliva samples to the genetic laboratory at Admera Health. Pharmacogenomic results will be sent directly to the research coordinator or a non-blinded research personnel in order to be sent to the investigational drug department at URMC.. Pharmacogenomic results will include a pharmacogenomic algorithm with color codes of genetic profiles and medication recommendation. Recommendations are broken down into 5 categories including: 1) consider alternative; 2) proceed with caution; 3) normal response expected; ~~4) increase dose and 5) decrease dose~~. For purposes of this clinical trial we will ignore the last two options. Additionally, these results will include other relevant information including: a) subject's phenotype (metabolic enzyme rate); b) genotype (allele function including decreased, increased, deletion, among others) and c) a clinical description of phenotype and genotype.

4.1. Treatment Dosage and Administration

Eligible patients will be randomized into 1 of the following 2 treatment groups:

- **Group A:** Experimental group. Based on immediate phenotypic results these subjects will receive pharmacogenomics guided prescription of ibuprofen (400mg) or acetaminophen (650mg) single dose for impacted third molar postoperative pain management. **(figure 3)**
- **Group B.**
  This group will receive the standard of care for impacted third molar postoperative pain with hydrocodone/acetaminophen (Norco®5mg/650mg) single dose.

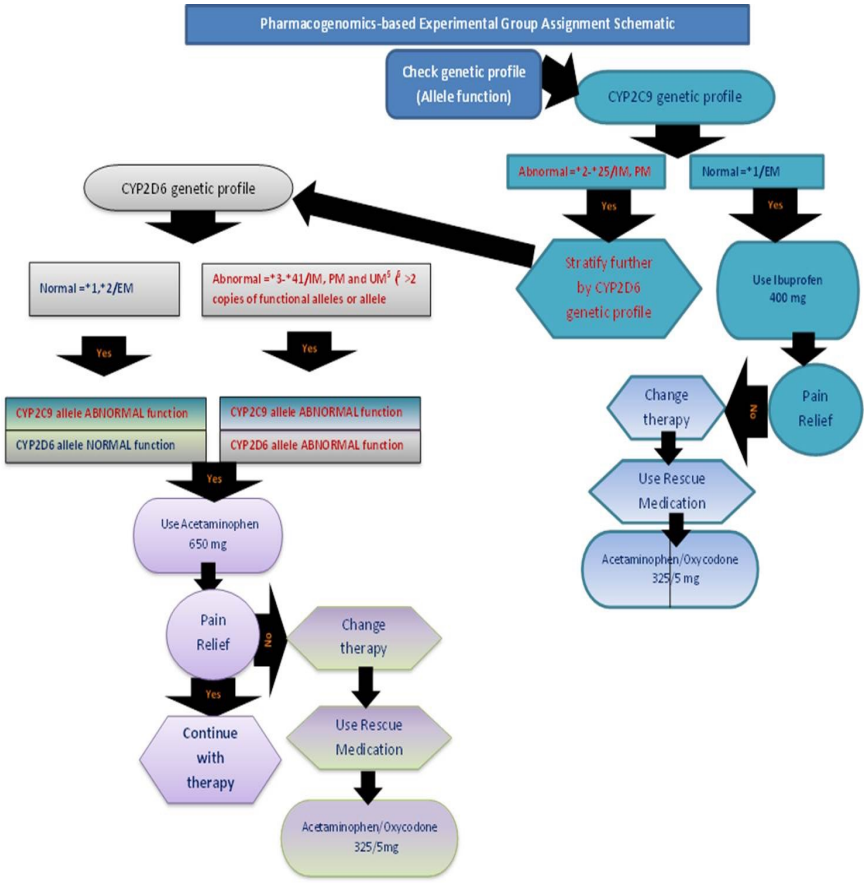


Figure 3. Representative of algorithm use for medication selection in experimental group. Rescue medication will be administered only if first-line-analgesic medication is not effective

Rescue medication. (figure 3) Oxycodone/acetaminophen (Percocet® 5mg/325mg) single dose will be administered if the first-line-analgesic prescription does not provide adequate analgesia. It is important to note that acetaminophen doses will be in the range of 650-975mg (i.e. below the recommended maximum of a 1000mg 'single' dose) if rescue medication is used on those subjects who will receive either acetaminophen (650mg) or Norco® (hydrocodone/acetaminophen; 5/650mg). The use of Percocet as rescue medication will assure that patients are not in risk of suffering postoperative pain (please see guidelines in figure 3.

4.2. Efficacy Assessments

Primary outcome. Comparison between pain control outcomes over the 6-hour period following receipt of pharmacogenomic testing guided prescription of non-opioid medication and those of standard of care with opioid analgesics.
Primary endpoint: Subject's success in pain relief over the 6-hour period post-intervention.
Secondary outcome. Examine the occurrence of meaningful change of drug regimen
Secondary endpoints. 1) Subject's metabolic enzyme rate (phenotype) known to affect a non-opioid medication identified by pharmacogenomic testing; 2) subject's success in responding to pain relief without drug substitution or discontinuation over a 6-hour period post-dosing.

4.3. Safety Assessments

Number of drug related adverse events over the 6-hour post-dosification period for pain control.

Adverse events (AEs) (if present)
AEs will be tabulated by treatment group, body system, and preferred term, AEs will be tabulated and analyzed by Fisher's Exact test to determine if the is an overall treatment effect. AEs will be summarized separately for all drug-related AEs, severity, and severe adverse events.
Definition of drug-related AEs in this study is an AE that follows a reasonable temporal sequence from administration of the used drug ; follows a known response pattern to the specific drug ; and, when appropriate to the protocol, is confirmed by improvement after stopping the used drug (positive dechallenge) and by reappearance of the reaction after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the patient's clinical state or by other therapies.
Severity of AE is defined in this study as the intensity of an AE, which is measured as follows: 1) mild; does not interfere with routine activities, 2) moderate; interferes with routine activities, 3) severe; patient is unable to perform routine activities.
For the purpose of this study AEs are defined as any sign, symptom, syndrome, or illness that occurs or worsens during the use of any analgesic or narcotic regardless of causality. A medical condition that is present when the patient enters the study is not defined as an AE unless this medical condition worsens after patient received the medication during the study. All AEs occurring during the 6 hours after dosing with medications used in this study will be recorded on the CRFs . All AEs must be followed by the Investigator(s) until resolved or until a stable status is achieved. AEs that occur after the patient is discharged from the study will not be recorded, unless they are determined to be serious adverse events (SAEs). SAEs will be recorded for 6 hours post dosing. SAEs include: 1) death, 2) a life threatening AE, 3) inpatient hospitalization or prolongation of existing hospitalization, and 4) a persistent disability/incapacity. In addition, relevant medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

In the event of a SAEs or death associated with the study that relates to the rights, safety, or welfare of the research participant the Investigator(s) must contact the RSRB immediately by telephone/telefax and follow up with a written description of the circumstances surrounding the event within 24 hours. Any SAEs occurring in a patient receiving any medication in the study or during the 6 hours following discontinuation of the medication must be reported to the Monitor and RSRB within 24 hours. Initial SAEs reports may be made by telephone, the originals copy of the completed SAEs Report Form (provided in the patients CRFs) must be sent to the RSRB by telefax.
All additional follow-up evaluations must be reported to the Monitor and RSRB. Such data should be sent to the RSRB by telefax within 10 working days after occurrence of the SAE or as soon as available. If

required, the Investigator will file the Safety Report with the appropriate regulatory authorities.

4.4. Assessment of Subject Compliance

The investigators or study coordinator will instruct all study patients in completion of these scales prior to surgery or following surgery but prior to dosing. All efficacy scores will be marked on the source document by study subjects and under the supervision of study personnel. The study coordinator or designee will only transcribe the patient's Baseline and Post-baseline period scores onto the CRFs.

4.5. Data & Specimen Banking for Future Research Use

Data and specimens will be banked for future research use for the purpose of future analysis in other genes related to variability of analgesic responses associated with acute surgical pain. These specimens will be stored in de-identified Eppendorf tubes at Admera Health laboratories under standard of care protocols to store DNA samples. Only study personnel related to this clinical trial will have access to these data/specimens. The time to keep this data is not estimated because new genes related to acute surgical pain in the human genome are still pending to be identified.

4.6. Genetic/Genomic Research Activities

Genotyping Procedures.

CYP2D6 and *CYP2C9* will be genotyped using the Luminex xTAG system. Relevant regions will be amplified using PCR (polymerase chain reaction) and clarified using Exonuclease I and Shrimp Alkaline Phosphatase. Individual mutations will be identified using allele-specific primer extension primers tagged for hybridization to Luminex xTAG beads. The following *CYP2D6* and CYP2C9 alleles will be identified: *1,*2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41 and duplication.

Single nucleotide polymorphisms identification and frequency.

This test is performed by next generation DNA sequencing. It is a primary measure of gene-drug interaction and genomic status. This test has shown increase clarity of the implications of genotyping for both clinicians and patients.

Target genotypes identification and frequency

This next generation of DNA sequencing test evaluates relevant regions to identified individual mutations in the three different cytochrome P40 alleles, studied in this proposal including allele 1, allele 2, and allele 3.

4.7. Costs to the Subject

The subject or the subject's insurance will be billed as a result of standard of care procedures associated with impacted third molar surgical removal. No additional costs will be incurred in regards to the pharmacogenomic or genomic test for the research participants. This pharmacogenomic test and analysis are covered by departmental funds at general dentistry and by Admera Health laboratory's research funds.

4.8. Payment for Participation

Subjects will receive one payment of fifty dollars ($50.00,) after completion of the study, in the form of a check.

4.9. Return of Individual Research Results

Genetic results will not be provided to the subjects at any time. However, incidental findings to adverse events will be managed according to the protocol guidance.

5. CONCOMITANT AND DISALLOWED MEDICATIONS

Antibiotics.
Prophylactic administration of penicillin V potassium (500mgs PO bid during 10 days) or clindamycin (300mg q6h PO during 10 days) antibiotics will be allowed in subjects undergoing surgery at the surgeon's discretion.

Antiemetics.
In the event that the investigator estimates postoperative nausea and vomiting require management with an antiemetic, the non-phenothiazine compound Tigan® (trimethobenzamide hydrochloride) will be permitted (250mg PO 3 times daily). Emesis will be recorded as an AE.

Ice Packs.
Ice packs to the affected area of the face and jaw will be allowed 2 hours after dosing with medication(s), however, will not be used prior to that time. Ice packs will be removed at least 15 minutes prior to any scheduled pain assessments. The use of ice will be recorded in the individual's source record and transcribed onto case report form by the study coordinator of any other designee.

Anesthetics.
Surgery will be performed under local anesthesia block(s) (for instance, 2% lidocaine, etc.). Light sedation under Nitrous Oxide may be used as required according to standard of care clinical practice. Precluded agents are all other sedatives or hypnotic agents, and all other local anesthetics.

Rescue medication.
Individuals in all groups will be administered Percocet® (oxycodone/acetaminophen, 5/325 mg single dose) as rescue medication. Rescue medication will be prohibited within the first hour after dosing with first line analgesic therapy.

6. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms and verbally that they have the right to withdraw from the study at any time without prejudice. Subjects could be withdrawn by the investigator, in circumstances including non-compliance, termination of funding, worsening of the disease under study, inter-current illness, pregnancy, lost follow up, etc.. No additional study activities will be completed after subject withdrawal from the study. Subjects withdrawn from the study will not be replaced.

7. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

7.1. Study Drug/Device/Biologic

Admera Health has developed an innovative pharmacogenomics test that addresses major healthcare issues resulting from individual genetic variability and subject's medication responses. PGxOne™, Admera Health's pharmacogenomic test, analyzes 13 well-established genes involved in drug absorption, metabolism, and activity. The test utilizes next generation sequencing technology and provides information for individual patient responses to 76 FDA approved drugs.10* All drugs covered by PGxOne™ have been endorsed by the FDA (Food and Drug Administration), EMA (European Marketing Authority), and/or the CPIC (Clinical Pharmacogenetics Implementation Consortium), an organization that provides clinical guidelines and recommendations on pharmacogenomics. See product white paper for additional information on the pharmacogenomic test/algorithm utilized in this study.

7.2. Dosage of Study Drug/Biologic

Not applicable for this study

7.3. **Subject Enrollment/Randomization**

Enrollment.
Subjects will be recruited by collaborating with our large referral base at Eastman Institute for Oral Health, University of Rochester, N.Y. Both the General Dentistry and Dental Urgent Care departments have more than 300 local patients with diagnosis of partial or full bone third molar impaction. Healthy men and non-pregnant women 18 to 35 years of age, scheduled to undergo surgical removal of 1 or more impacted third molars, at least 1 of which must be a bony mandibular impaction, who have received only specified preoperative medications/anesthetics, who develop sufficient levels of pain (50 of 100mm on dental pain 100mm-visual analog scale) up to 6 hours after surgical removal, and who sign an informed consent form, will be enrolled in the study.

Randomization.
Following impacted third molar surgical removal, each individual will be assigned a unique, number in chronological order of admission into the study. Subject numbers are determined by a computer-generator-randomization-list generated by the research coordinator and correspond to the drug label number. A block-wise randomization will be used. See table below. The sequential number will be verified by a blinded person at Eastman Dental Center and from entries in the screening logs.

Treatment group	Participant Code	Treatment Description
A	participant initials and #1	Pharmacogenomic test guided pain medication prescription
B	participant initials and #2	Standard of care medication
A	participant initials and #3	Pharmacogenomic test guided pain medication prescription
A	participant initials and #4	Pharmacogenomic test guided pain medication prescription
B	participant initials and # 5	Standard of care medication
A	participant initials and #6	Pharmacogenomic test guided pain medication prescription
B	participant initials and #7	Standard of care medication

This table is an example of the block-wise randomization method will be utilized in this study. Participant codes are fictitious.

7.4. **Accountability of Investigational Supplies**

Masking (over-encapsulation methodology)
Not applicable for this study due to the variable in size and other dimensions of the tablets for the drugs used in the study

7.4.1 Blinding Methodology for Subjects

CODE	Phenotype	Medication q6-8h
A	Normal response (EG)	Ibuprofen (600mg)
B	N/A (CG)	Vicodin (hydrocodone/acetaminophen; 5/300mg)
C	Normal Response (EG)	Hydrocodone (5mg)
D	Normal Response (EG)	Acetaminophen (625mg)

Rescue Medication Code	Medication q6-8h
E	Percocet (oxycodone/acetaminophen; 5/325mg)

This table represents the codes of the study utilized to appropriately administer medication for this study. This table is going to be used by research pharmacists in order to send medication to dental clinic at Eastman Institute for Oral Health. Definitions; EG; experimental group. CG; control group

Figure 4. Representative of codes will be used for the research pharmacy department. Study codes will be used on prescriptions in order to assist blinding and masking of medications for both investigators and patient.

Unblinded investigators will administer the study medication to subjects who are blinded by way of wearing a mask over their eyes.

Research pharmacy and dental clinic procedures

The study investigators or sub-investigator will schedule intervention day/time. At that time, the investigator(s) will be responsible to send two medication prescriptions including both opioid formulation (hydrocodone/APAP) and (oxycodone/APAP) into the inestigational drug department at URMC to secure medication dispensing and stock. For over-the-counter medications a prescription is not needed. Pharmacogenomic testing will be carried out at the preoperative appointment. However, the results will be blinded to investigators.. The investigational drug department personnel assigned to this study will review pharmacogenomic testing results and choose study group and type of medication to be administered, according to randomization scheduled list. (Figure 4, below). On the day of surgery, the non-blinded research staff will pick up two different blister cards or medication containers (if applicable) that include; the first-line-analgesic medication and the rescue medication, from the investigational drug department. The medications will be packaged into envelopes or blister cards with appropriate information (if applicable) and study codes. Once the intervention is completed, and after the local anesthesia effect wears off, the subjects will be given their first dose of pain medication, by the non-blinded research staff. Subjects will remain in the dental chair and will be asked to complete two additional pain questionnaires (Pain Severity Rating and a Dental Pain Relief Rating). These questionnaires are to be completed at 15minutes (baseline), 30 minutes, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 5 hours, and 6 hours post-administration of pain medication. Subjects' vital signs will be monitored all the time during dental clinic stay, there is the possibility that subjects will feel drowsy or sleepy (medication effect). Investigators will measure vital signs and awake the patient to accurately assess pain. In addition, 3-4 minutes after taking the study drug the subjects will be given two stopwatches and asked to stop one when they feel the first sign of pain relief. They will also be asked to stop the 2nd stopwatch when they feel meaningful (feels much better) pain relief. At the end of the 6-hour-period, they will be asked to provide an overall evaluation of the study medication. They will then be dismissed from the study.

Subject Withdrawal of Study Drug

Subjects may stop the treatment in this study. However, they will not continue to be followed in this clinical trial.

7.5. Emergency Drug Disclosure

Identity of products used for this study

Because pain medication tablets will be packaged in blister cards (envelopes) consisting of 2 tablets (as appropriately indicated by Investigators) dosage units. The contents will be labeled with the, study code, protocol number, Principal Investigator number (if applicable), and directions for use. The information on these clinical supplies will be received and maintained by the research coordinator. Disclosure of the subject's medication information will be accessed only in the case that first –line-therapy is not effective or in a medical emergency. See section 4.3, adverse events, for appropriate

actions taken by the investigator in medical emergencies. In the case of a medical emergency the subjects will be withdrawn from the drug only.

8. SAFETY AND REPORTABLE EVENTS

8.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug. See section 4.3 for further definitions.

8.2. Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

8.3. Recording Adverse Events

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., drug or device), contributing factors, and any action taken with respect to the study drug/device.
Timeframe for recording AEs will occur 6 hours after dosing. Follow up of adverse experiences will be done until the event is resolved or stabilized including those that are ongoing/unresolved at the time of subject concluding study participation.

8.4. Responsibilities for Reporting Serious Adverse Events

The Investigator/coordinator will make every effort to record all serious adverse experiences that occur during the study period in the appropriate source documents and/or AE log as applicable. The study period for reporting serious adverse events will be indicated. AEs forms will be completed. The Investigator/ coordinator will comply with regulations and RSRB policy regarding the reporting of adverse events.

9. RISK/BENEFIT ASSESSMENT

9.1. Potential Risks

1) The subject may/will experience additional discomfort by delaying pain medication until the DPIS reaches 50mm out of 100mm; 2) The proposed algorithm method may result in less than optimal pain control; 3) there is a risk for inadequate pain control and 4) there is a risk for loss of

privacy/confidentiality.

9.2. Protection Against Risks

All subjects will be monitored for adverse events associated with the administration of opioids and saliva collection for genotyping. Subjects and legal representative(s) will be informed prior to each research intervention (saliva collection for genotyping and clinical data collection) during the study period. This may decrease the anxiety related to any inconvenience the subject may experience from these procedures in those subjects cognitively able to comprehend the provided information. Subjects will also be monitored for analgesia efficacy.

All saliva samples will be collected using standard of care procedures to minimize the risk of infection. Appropriate medical supervision will be available on a 24-hour basis to ensure that subjects are appropriately cared for and monitored throughout their participation in the study. Prior to discharge, patients will be given standard postoperative home care instructions about third molar extraction including how to contact general dentistry and dental urgent care nurses or physicians for any concerns regarding the patient's recovery at home. An investigator will also be available 24 hours a day, 7 days a week via a hospital operator.

Adverse events, serious adverse events (SAE's) and unanticipated events will be recorded in accordance with the IRB guidelines and documented in source materials and case report forms. For each occurrence, causality and relationship to drug will be documented and the information reported to the IRB as per standard operating procedures.

9.3. Potential Benefits to Subjects

Individual study subjects will not derive any direct benefit from participation in the study. We will make the genotype information and their implications available to patients who wish to know this information and have consented for the release of that information to them once we do our final analyses. In some cases individual subjects may benefit from this information if future surgical procedures are necessary. Patients presenting for surgical procedures in the future may benefit from the research if the models mapping genotype to pain response phenotype are predictive with the requisite precision.

9.4. Alternatives to Participation

Alternatives if the patient decides not to participate in this study include the standard of care of impacted third molar surgical removal w/o using pharmacogenomic testing for guided-acute surgical pain management.

10. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

All subjects screened and enrolled in this study will be identified by an assigned study number only. All study records will be maintained in a locked office. Information collected will be treated as confidential, as provided by law. The study records will be made available for review only to the Institutional Review Board. The subjects' names or any identifier will not be used in published information relating to this study.

To minimize potential risks to the subject's confidentiality, all protected health information will be collected in accordance with the HIPAA guidelines and a signed research authorization will be obtained

from the subject prior to enrollment. All study-related records will be kept in a secured research record room or the secured study coordinators office suite. These records will be available only to the research staff involved in the clinical research of the subject, and representatives from regulatory agencies. Subject confidentiality will be protected to the extent permitted by law. Data labeled with subject identifiers will not be released without the knowledge and consent of the subject. Electronic databases with subject identifier will also be user-access protected. All samples collected for analysis will be labeled with a coded subject number, sample identifier and date/time of collection. Subjects will not be individually identifiable by the subject number. Our data storage in locked cabinets and password protected computers and files will prevent unauthorized access, use, and disclosure of data, identifiers, and links to identifiers.

11. RESEARCH INFORMATION IN MEDICAL RECORDS

After completion of the study pharmacogenetic results will not be included in the medical record of each research participant. However, research related documentation for study participation and consent form will be included in the subjects' records.

12. DATA ANALYSIS AND MONITORING

12.1. Sample Size Determination

Assuming that a 15% reduction in pain outcomes signifies that the pharmacogenomics test has produced a significant effect, we will need 238 subjects total. 119 in each group to achieve 90% power at an alpha level of 0.05.

12.2. Planned Statistical Analysis

Specific Aim 1. (Pain control outcomes)
Pain Severity Rating **(SPID)**, Dental Pain Relief Rating **(DPRR)** and Onset of Perceptible and Meaningful Relief on 12 hour period.

The primary analysis will assess the change in the pain severity rating, measuring the time-weighted sum of all observations (SPID) over the entire 6 hour period. This will be analyzed by comparison among the 2 groups, using ANCOVA model with factors for treatment, sex, Baseline pain intensity score and treatment-by-Baseline pain intensity score interaction.

Dental Pain Relief Rating (DPRR) will be analyzed in three ways including 1) The time-weighted sum of all observations (TOTPAR) over the first 6 hours of treatment and 2) the entire 12-hour period for comparison among the two groups, using ANCOVA model with factors for treatment, sex, Baseline pain intensity score, and treatment-by-Baseline pain intensity score interaction and 3) individual scores at each evaluation period will be analyzed for comparison between the 2 groups using ANCOVA model with factors for treatment, sex, Baseline pain intensity score, and treatment-by-Baseline pain intensity score interaction.
Finally, relief scores associated with the onset of perceptible and meaningful relief will be analyzed for comparison among the 2 groups the two groups, using ANCOVA model with factors for treatment, sex, Baseline pain intensity score, and treatment-by-Baseline pain intensity score interaction.

Onset of Perceptible and Meaningful Pain Relief. Time to onset of perceptible and to meaningful pain relief product-limit (Kaplan-Meier) survival curves will be analyzed for comparison among the 2 groups using log-rank test. Time to onset of perceptible and meaningful pain relief will be assessed by each group using the stopwatched method. For patients who drop out, the time to onset of perceptible and meaningful pain relief will be censored at Hour-6. For patients who take rescue medication before

reaching time to onset of perceptible and meaningful pain relief, the time to relief will be assigned and event time (in hours) 6.1 + 0.1/(time rescue medication was taken -time selected medication was taken). This rule for handling data for patients that took rescue medication affects only upper limit to the confidence interval. Multiple comparisons between groups will be performed if a significant treatment effect exists.

Time to rescue medication. Time to rescue medication product limit (Kaplan-Meier) survival curves will be analyzed for comparison among the 2 groups using log-rank test. For patients who remain in the study and do not take rescue medication within 12 hours, the time will be censored at Hour-12. Multiple comparisons between the 2 groups will be performed if a significant treatment effect exists.

Overall Global Evaluation. Global evaluation scores will be analyzed for comparison among the 2 groups, using ANCOVA model with factors for treatment, sex, Baseline pain intensity score, and treatment-by-Baseline pain intensity score interaction.

Specific Aim 2. (Opioid analgesics prescription reduction)
We will examine the number of patients receiving standard of care with opioid analgesics and those receiving pharmacogenomic-testing-driven-prescribed medications. We will use Fisher's exact test analysis in this specific aim.

Other secondary analysis includes:
Vital signs and demographics.
Vital signs, including blood pressure, heart rate, oral temperature, and respiratory rate, will be summarized at Baseline and during the post-dosing period. Demographic data will be compared statistically to assess the treatment group comparability at Baseline. Variables with continuous distribution (i.e., age, etc.) will be analyzed by analysis of variance (ANOVA). Categorical data (i.e., sec, race, etc.) will be analyzed by the chi-square test with Yates' correction. Baseline pain severity will be analyzed by ANOVA.

12.3. Data and Safety Monitoring

This is a clinical trial with not minimal risk to participants. All expected adverse events are related to the standard of care administration of local anesthesia and pain relief medications for the planned surgical procedure and are recorded as part of the patient record. Adverse events will be recorded in the patient's study record, assessed for relatedness and reported to the IRB on determination that they meet IRB criteria for reporting. Hans Malmström, DMD will monitor this study for safety issues related to the participating subjects.

13. REFERENCES

1. Denisco RC, Kenna GA, O'Neil MG, Kulich RJ, Moore PA, Kane WT, et al. Prevention of prescription opioid abuse: the role of the dentist. Journal of the American Dental Association. 2011; 142(7):800–10. PMID: 21719802.
2. National Institute on Drug Abuse. Topics in Brief: Prescription Drug Abuse—A Research Update from the National Institute on Drug Abuse. National Institute of Health, 2011 December 2011. Report No.
3. Hersh E.V, Kane W.T, O'Neil M.G, Kenna G.A, Katz N.P, Gulobic S, Moore P.A. Prescribing Recommendations for the Treatment of Acute Pain in Dentistry. Compend Contin Educ Dent. 2011 Apr; 32(3):22, 24-30; quiz 31-2.

4. Qi D.S, May L.G, Zimmerman B, Peng P, Atillasoy E, Brown J.D, Cooper S.A. A randomized, double-blind, placebo-controlled study of acetaminophen 1000 mg versus acetaminophen 650 mg for the treatment of postsurgical dental pain. Clin Ther. 2012 Dec;34(12):2247-2258.
5. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers—-United States, 1999–2008. MMWR—Morbidity & Mortality Weekly Report. 2011; 60 (43):1487–92. PMID: 22048730.
6. Rasubala L, Pernapati L, Velasquez X, Burk J, Ren Y-F. Impact of a Mandatory Prescription Drug Monitoring Program on Prescription of Opioid Analgesics by Dentists. PLoS One. 2015; 10(8): e0135957.
7. Barden J, Edwards JE, McQuay HJ, *et al*. Attenuation of pain in a randomized trial by suppression of peripheral nociceptive activity in the immediate postoperative period. Anesth Analg. 2002; 95(5): 1351-1357.
8. Cooper SA. Comparative analgesic efficacies of aspirin and acetaminophen. Arch Intern Med. 1981;141(3): 282-85.
9. Moore P.A, Nahouraii H.S, Zovko J.G, Wisniewski S.R, Dental Therapeutic Practice patterns in the U.S. II. Analgesics, corticosteroids, and antibiotics. Gen Dent. 2006; 54(3):201-207.
10. Tufts Health Care Institute Program on Opioid Risk Management. Executive Summary. The Role of Dentists in Preventing Opioid Abuse. Tufts Health Care Institute Program on Opioid Risk Management 12th Summit Meeting. March 11-12 2010. Available at www.thci.org/opioid/mar10docs/executivesummary.pdf. Accessed January 20 2016.
11. Ren Z-Y, Xiu X-Q, Bao Y-P, He J, Shi L, Deng J-H, Gao X-J, Tang H-L, Wang Y-M, Lu L. The Impact of Genetic Variation on Sensitivity to Opioid Analgesics in Patients with Postoperative Pain: A Systematic Review and Meta-Analysis. Pain Physician 2015; 18:131-152.
12. Uribe-Rivera A, *et al.* Predictive genomics to personalize opioid analgesia in oral and maxillofacial surgery. Translational Science 2015. Abstract/Poster presentation.
13. Neunzig I, Göhring A, Drăgan C-A, Zapp J, Peters F.T, Maurer H.H, Bureik M. Production and NMR analysis of the human ibuprofen metabolite 3-hydroxyibuprofen. J Biotechnol 2012 Feb 27; 157(3):417-20.
14. Hamman MA, Thompson GA, and Hall SD (1997) Regioselective and stereoselective metabolism of ibuprofen by human cytochrome P450 2C. Biochem Pharmacol 54:33– 41.
15. Mazaleuskaya L.L, Theken K.N, Gong L, Thorn C.F, FitzGerald G.A, Altman R.B, Klein T.E. PharmGKB summary: ibuprofen pathways. Pharmacogenet Genomics. 2015 Feb; 25(2):96-106.
16. Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet. 1998 Feb; 34(2):101-54.
17. Lloyd MD, Yevglevskis M, Lee GL, Wood PJ, Threadgill MD, Woodman TJ. α-Methylacyl-CoA racemase (AMACR): metabolic enzyme, drug metabolizer and cancer marker P504S. Prog Lipid Res. 2013; 52: 220–230.
18. Jiang Z, Fanger G.R, Woda B.A, Banner B.F, Algate P, Dresser K, Xu J, Chu P.G. Expression of alpha-methylacyl-CoA racemase (P504s) in various malignant neoplasms and normal tissues: a study of 761 cases. Hum Pathol. 2003 Aug; 34(8):792-6.
19. Qu X, Allan A, Chui G, Hutchings T.J, Jiao P, Johnson L, Leung W.Y, Li P.K, Steel G.R, Thompson A.S, Threadgill M.D, Woodman T.J, Lloyd M.D. Hydrolysis of ibuprofenoyl-CoA and other 2-APA-CoA esters by human acyl-CoA thioesterases-1 and -2 and their possible role in the chiral inversion of profens. Biochem Pharmacol. 2013 Dec 1; 86(11):1621-5.
20. Sakaguchi K, Green M, Stock N, Reger T.S, Zunic J, King C. Glucuronidation of carboxylic acid containing compounds by UDP-glucuronosyltransferase isoforms. Arch Biochem Biophys 2004; 424: 219–225.
21. Martin B.K, Meinert C.L, Breitner J.C.S. Double placebo design in a prevention trial for Alzheimer's disease. Controlled Clinical Trials 23 (2002) 93–99.