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A DNP PROJECT

DEMYSTIFYING PHARMACOGENOMIC IMPLICATIONS FOR THE ANESTHESIA PROVIDER

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Abstract

Anesthetic management of a patient is an art that cannot be delivered in just one fashion. There is a multitude of variants that come into play, from the patient's medical history, medication regimen and current physical state. There is one more important aspect that is of note, and that is an individuals' pharmacogenomics. Understanding this concept could lead to a better understanding of the patient's genetic predispositions to medication metabolism. Anesthesia providers are lacking information and knowledge regarding pharmacogenomics and its utility in managing their patients. The audience that we reached with this project were physician and nurse anesthesiologist as well as resident registered nurse anesthetists (RRNA). Offering an educational presentation to anesthesia providers regarding the utility of pharmacogenomics as well as how to interpret its results could lead to a better understanding and incorporation of pharmacogenomics into anesthetic practice. The ultimate aim was that anesthesia providers gain more awareness about pharmacogenomics and seek to educate themselves further on the topic in order to themselves incorporate it into their anesthetic practice.

Keywords: pharmacogenomics, pharmacogenetics, precision medicine, tailored medicine, genetics, cytochrome enzyme, drug metabolism, poor-metabolizer, ultra-metabolizer, anesthesia allele: variants, single-nucleotide polymorphism

Demystifying Pharmacogenomic Implications for the Anesthesia Provider

Pharmacogenomics (PGx) is a method of analyzing the response of a person to medications with regard to the genetic code. This paper aimed to explore the significance of incorporating pharmacogenomic testing into a tailored anesthetic management plan. Initial implementation began with identified high risk populations such as autoimmune disease patients, though it has the potential of global incorporation in the pre-admission testing of every patient undergoing anesthesia. Pharmacogenomic testing is already in use for many cardiac and psychiatric patients including many divisions of the Mayo Clinics, Shands Hospital in association with University of Florida and the Cleveland Clinic (van der Wouden et al., 2017). These facilities have implemented a PGx based personalized medicine center to better serve their patients, and have exhibited improved patient outcomes. This benefits the patient by reducing or eliminating the trial and error associated with medication management to find a suitable dose for a desired response, which can cost the patient time and money. Anesthetic practice is governed by administering medications that the patient may never have come in contact with prior. Knowing which medication and what dose is required for the desired effect is of the utmost importance throughout the operative period. A tailored management plan unique to each patient's genetic code not only provides for a safer anesthetic but more predictable outcomes as well. Pharmacogenomics can also be considered as an incentive tool for hospitals to attract patients and improve the healthcare business as a whole.

Background and Significance

To understand the importance of pharmacogenomics and its potential place in anesthesia management we first need to understand what it is and how this will affect us. Pharmacogenomics is an area of study that examines the genetic code of patients and identifies

polymorphisms (variants) in that code that can affect the metabolism of 70% to 80% of the medications patients are currently prescribed (Ama et al., 2017). Specific to anesthesia many of the medications administered during the operative periods are affected by the cytochrome P-450 (CYP-450) enzyme cascade relative to the Phase 1 metabolism. The CYP-450 class of microsomal enzymes is the primary avenue for reduction, oxidation and hydrolysis that form inactive metabolites and allow excretion of numerous anesthetics delivered on a daily basis. Pharmacogenomic testing allows us to see if a patient is an ultra, intermediate or slow metabolizer. Knowing this information allows anesthesia providers to anticipate how a patient will react to a specific drug being administered, regardless of its dosing (Saba, Kaye & Urman, 2017). Looking first at an ultra-metabolizer (UM), this means that the patient will metabolize a certain drug more quickly than expected. Subsequently, the drug will have a shorter duration of action and ultimately a sub optimal desired effect. Conversely, a poor metabolizer (PM) will have the reverse effect, where this patient will require an extended period of time in order to metabolize this drug. This leaves the patient at an increased risk for developing adverse drug reactions including slowed onset and extended effect (Ama et al., 2010).

To better understand this concept, we can examine a specific scenario, looking at patients identified as slow metabolizers and the enzyme CYP2D6. This patient would not be able to convert codeine into morphine. Being unable to make this conversion, this patient would not receive the desired pain relief yet would be more susceptible to the side effects of the drug. Contrariwise, an ultra-metabolizer given the same dose of the prodrug codeine, will metabolize this at an exponential rate into morphine, which has the potential for overdose relating to the additional speed of metabolism. These alterations of the allele that controls the actions of the CYP2D6 are referred to as polymorphisms. The gene polymorphism CYP2D6*2 allele occurs

most frequently in the North African, Ethiopian and Arab populations between 16% to 28% of the time (Lexicomp, 2019). This means people of these ethnicities are more likely to have an adverse reaction to either morphine or codeine. A normal 30 to 60-minute onset of action via normal metabolism from the prodrug codeine into morphine could be 6-10 minutes. This effectively increases the amount of morphine in the system to dangerously high levels causing apnea or profound mental impairment. Pharmacogenomics testing delivers information regarding a patient's metabolism, whether slow, intermediate or ultra to the anesthesia care provider (Ama et al., 2010).

Introducing the use of pharmacogenomics into standard practice will allow the anesthesia provider to offer a more individualized anesthetic plan; focusing not only on the patient's medical history but having a more profound understanding of the patient's ability to metabolize certain drugs. This permits the provider to tailor the anesthetic plan to the patient's specific needs and determine the utilization or omission of certain drugs. Post-operative pain management is also an area that could benefit from the incorporation of pharmacogenomics. If an anesthesia provider knows that a specific patient is susceptible or resistant to a particular medication, the anesthesia provider can research a more appropriate medication or adjust the dose accordingly in order to provide the best pain control possible. Consequently, a patient not only benefits from adequate pain control, which is one of the anesthetic goals, but patient safety has also been optimized (Kiley, 2017). Cohen, Sadhasivam and Vinks (2012) state that utilizing pharmacogenomics in anesthetic practice would decrease the occurrences of post-operative adverse drug reactions. Integrating pharmacogenomics into the anesthetic management of a patient would ensure superior patient outcomes. This would also minimize the burden and

negative impact that adverse drug reactions have on the hospitals and society as a whole (Cohen et al., 2012).

The United States Food and Drug Administration (FDA) declares that there are over 2 million severe adverse drug reactions (ADR) every year. They also have found that these ADR are the fourth leading cause of death in the United States. These ADR are found to be the cause of harm or death to 1 in 5 patients. The FDA has claimed that ADR cost $136 billion a year. This exorbitant amount comes from the culmination of extended hospital stays, and death directly related to these ADR (Ama et al., 2010). The data provided infers that post-anesthetic recovery time could be minimized, facilitating the speedier admission and discharge of patients from the post-anesthesia care unit (PACU). Prescribing the suitable amount of opioid narcotic medication to a patient rather than a blanket prescription enables anesthetic providers to abate their contribution to the opioid epidemic. The ADR requiring intervention with naloxone or flumazenil could be eradicated and the enticement of an institution trying to market its services could be impressively enhanced with the offer of safer and genetically precise patient management.

Needs Assessment

The incorporation of pharmacogenomics testing has already been broached with anesthesia providers. The main recurring concern from these providers is the lack of comfort with interpretation of the results of a PGx test. Various physician specialties don't fully comprehend what the testing actually signifies including how the results can be interpreted and best integrated into their patient care. However, many have stated that they feel PGx testing would be beneficial to their patients, though it is drastically underutilized. The universal conclusion points to the need for more education for anesthesia providers regarding

pharmacogenomic testing and how to best interpret the results for the optimal benefits for their patients (Heale et al., 2017).

Understanding the growing popularity of PGx and personalized medicine, we can prove that the use of pharmacogenomics can affect a variety of patients and generations with the help of a few particular examples. Post-operative nausea and vomiting (PONV) is a frequent side effect from anesthesia that anesthesiologists attempt to combat with the administration of anti-emetics such as ondansetron. Saba et al. (2017), explain that the deletion of certain polymorphisms, like the -100_-1-2AAG decreases the effectiveness of ondansetron to prevent PONV by 35%. Another example of pharmacogenomics effects on anesthesia is the frequency of pediatric emergence delirium. Delirium is a common post-anesthetic reaction, especially in the pediatric population. As stated by Cohen et al. (2012), when volatile anesthetics were used children found to have a specific AA genotype had an increased incidence of emergence delirium than those that did not possess this AA genotype.

In this real-life scenario, the patient was a lactating mother who happens to have been an ultra-metabolizer with two or more functioning alleles of the CYP-2D6(*2) microsomal enzyme. This new mother was given codeine on the labor and delivery floor to manage her post-partum pain. However, being an ultra-metabolizer, she converted the codeine into morphine at a much higher rate than would normally be expected. This particular case led to the infant's death because of a morphine overdose the mother administered to her infant through the breast milk (Ama et al., 2010). Although this is an extreme illustration, this validates the fact that PGx testing has a role in all levels of medical practice, not simply for anesthesia purposes but for the overall medical care of the global patient population.

Looking at the extensive damage that can occur because of ADR we postulated that incorporating pharmacogenomic testing into a standard pre-operative evaluation can lead to significantly decreased incidence of these adverse events. In turn, this can provide maximal patient safety and enhanced satisfaction for both patients and providers. All while decreasing the encumbrance of elongated recovery time that plagues hospitals, communities and society as a whole.

Problem Statement

Patient outcomes suffer from the lack of knowledge readily obtained from pharmacogenomic testing. The wide variety of patients coming to the hospital for differing surgeries everyday can be the most dangerous high acuity and critical care scenarios presented to anesthesia providers. The pre-operative evaluation is only as complete as the information received from the patient, family and medical record. These records are often deficient or lacking specifics for the operative patients' needs during anesthesia. Incorporating pharmacogenomics as a supplemental addition to the available information could provide vital insight into patient care, especially for higher risk populations such as patients in the ASA 3 or above categories or those with connective tissue disorders, autoimmune disorders or congenital anomalies.

The information that is obtained from a pharmacogenetic profile for these patient populations could provide for appropriate pain relief with a specific genetic medical profile that optimizes pain control and minimizes adverse reactions. These practices are tested once in a patient's life and the results are easily conveyed to any healthcare provider with an email, printout or even a wallet card (Genetics Testing, 2019). The changes to patient care are followed throughout the operative period and beyond, providing an unequivocal level of safety and

accuracy in medication administration that ensures the greatest possible outcome that is genetically tailored to each patient.

The clinical question postulated of anesthesia providers is; would a didactic educational presentation alleviate concerns of anesthesia providers regarding implementation and interpretation of pharmacogenomic testing into current anesthetic practice?

Aims and Objectives

A recurring theme while researching pharmacogenomics testing was that although it has been shown to provide invaluable information regarding a patient's genetic profile and metabolism of drugs, it is severely underutilized. A handful of hospitals across the country have incorporated this into their pre-surgical testing (Cohen et al., 2012 & van der Wouden et al., 2017). However, there is a substantial lack in the education regarding the interpretation of pharmacogenomic profiling and how providers can utilize these results to enhance patient care outcomes.

This project aimed to fill the gap that exists regarding the inadequate education of pharmacogenomics. This provided anesthesia professionals with a better understanding of what encompasses pharmacogenomics and how to interpret the results. Another aim was to survey anesthesia providers following edification, to ascertain their willingness to incorporate pharmacogenomics testing into the anesthetic management of their patients with the resources presented.

Our primary objectives based on the aims above, have been identified as the following:

1. Pre-educational intervention survey of anesthesia providers regarding their base knowledge of pharmacogenomics.

2. Supply anesthesia providers with a didactic presentation focused on addressing shortcomings of pharmacogenomic education utilizing:
    a) An in-person PowerPoint presentation.
3. Post-educational intervention survey of anesthesia providers having newly acquired knowledge of pharmacogenomics based on the educational supplement.
4. Evaluate the anesthesia provider's preference for the multi-modal didactic presentation as a means of pharmacogenomic education.
5. Evaluate the demographic information in the surveys for trends of acceptance or rejection of the incorporation/utilization of pharmacogenomics into their practice categorized by the following:
    a. Age of provider.
    b. Years of practice.
    c. Level of education.
    d. Type of provider.

Once the information was gathered and analyzed, we extrapolated a formal understanding of anesthesia providers' mindset regarding the incorporation of pharmacogenomics testing into their anesthetic plan. Based on this information we can advocate for the incorporation of pharmacogenomic testing into standard pre-operative evaluations of patients.

This project commenced in January of 2019 with the preliminary research and concluded at the end of February of 2020 with project proposal defense. The implementation of the project occurred twice in July of 2019 and once in October 2019. After that, the data was analyzed and summarized into study findings and a final version of the DNP project was drafted and defended on January 27, 2020.

Translation Theory

The evidence translation theory that best fits the framework of our project was focused down and modified to Rogers's theory of innovation diffusion (Appendix 1). The first part of the base theory (Appendix 2) suggests that there are five types of adopters and five stages of adoption into practice. Specifically, the innovation theory suggests adoption of new ideas initially through innovators that bring the alternatives of practice to a department, in this case directly to the anesthesia providers. Some members will adopt new ideas/practices with delight, embracing the adjustment while others will see the change as an additional complication to their standard practice and reject it completely or until mandated to assimilate.

The second portion of the theory regards the diffusion of the innovative practice. This is the method that implementation follows during a rollout process. This is done through the education and persuasion of the general body of anesthesia practice and hierarchy convincing them through evidence-based research, guidelines and potential cost savings to adopt the new standard into practice. This would be followed by moving steadily toward the decision to implement the new innovation. The implementation process would be another phase executed to assess the changes in practice and provide data for a validation of continued utilization. As with many other strategies there would be a confirmation with regards to its incorporation into practice with occasional reevaluation of intricacies to streamline processes, intensify usage or even propose viable alternatives.

Specifically, this project follows the Rogers's evidence-based framework model to initiate change in practice through education and dissemination of knowledge in order to persuade, in this case, the anesthesia providers to accept pharmacogenomic testing for scheduled

operative procedures. This would provide additional information regarding anesthetic medication administration. The educational portion would illustrate the benefits of pharmacogenomics testing and the resources available as well as simplified interpretation of data to aid with assimilation of the new information into everyday practice.

This model is appropriate for this project as the information regarding PGx is not new. Nevertheless, healthcare system utilization has been delayed because of obstructions associated with a powerful lack in understanding of pharmacogenomics and the inability to effectively interpret its results. The cost of PGx testing has constantly been a significant barrier for healthcare providers to overcome. Additional information regarding the cost/benefit ratio of pharmacogenomics testing and storage versus the cost of adverse drug reactions will also be highlighted. This can improve understanding and potentially move an organization toward pharmacogenomics testing for specific populations with a potential for universal incorporation.

Review of Literature

The literature review began with broad search terms encompassing pharmacogenomics, anesthesia, precision care, tailored medicine and adverse drug reaction. The research process is clearly defined within the Prisma table (Appendix 3). The net casted was initially wide relating to a greater need for understanding of what pharmacogenomics entails. Once an understanding of this concept was acquired, a more narrowed search began, focusing on the role of PGx and variable medication metabolism. This offers a possibility of changing how a provider cares for their patients with the use of precision medicine. This level of research emphasized the significant number of barriers between conceptual pharmacogenomics and its practical integration into medical practice. This is especially evident in the intricate practice of anesthesia.

Described below are the varying barriers and main points that became evident during this research process (Appendix 4).

Introduction, Education & Background

Early in the research process, there were trending points of interest and specific topics of study that became evident. In order to understand and explore all of these options, an understanding of the base concepts of pharmacogenomics is essential. Searle et al. (2009) states that along with the discovery of the role that single nucleotide polymorphisms play on drug metabolism and its effects, in accordance with the Human Genome Project, an understanding of what this discovery means and how to better interpret such findings was evident. The product of the Human Genome Project helps explain how certain people can be either ultra, intermediate, extensive or slow metabolizers. These are best defined by Ama et al. (2010) and Saba et al. (2017), where an ultra-metabolizer would be more inclined to developing signs of an overdose when given a prodrug like codeine that would metabolize into the active metabolite morphine. Inversely, a slow metabolizer will exhibit an absence of overdose symptoms as well as a lack of any pain control. Some of the most commonly studied cytochromes and genes that yield the most information in terms of drug metabolism and effect are polymorphisms of CYP-450 genome. Specifically, pain medications are metabolized primarily by CYP-3A4 and CYP-2D6, as well as catechol-O-methyltransferase (COMT). Pain medication is a major classification involved in anesthesia, is highly involved in patient care outcomes and is directly related to ameliorating patient satisfaction. Chidambaran et al. (2017) and Landau et al. (2012) explain the effects that CYP-2D6 and CYP-3A4 have on the metabolism of drugs based on an individual patient's response directly related to their abilities to metabolism through these processes. Chidambaram et al. (2017) continues to explain that an appreciation of these variations and incorporating

pharmacogenomics for a better understanding of individual responses would lead to enhanced pain management in the peri-operative period and in turn an increase in overall patient outcomes and satisfaction. The aforementioned authors have stated that the use of pharmacogenomics would benefit medicine from the standpoint that the more information one has regarding a patient, the more tailored of a regimen we can offer said patient and offer the best and most optimal care available. Using this technology to further develop an anesthetic plan is touched upon, especially when some of the main focuses emphasized by these authors are the concerns of post-operative nausea and vomiting (PONV), malignant hyperthermia (MH) and pseudocholinesterase deficiencies. These are expressly correlated with the administration of anesthetics and their potential effects on a patient.

Barriers to Pharmacogenomics

Multiple barriers have arisen during the research process in regard to pharmacogenomics. The barriers that stand out the most and have raised the greatest concern are those regarding liability and privacy. Marchant et al. (2008) and Riddle et al. (2016) describe this in their research as being one of the major drawbacks to incorporating pharmacogenomics into formulating a more custom-made medical or anesthetic plan for the patient. Marchant et al. (2008) have raised through their research some important questions. In regard to how we can ensure that this private information is stored in such a way that it will not be accidently disseminated into the world and/or distributed without the patient's knowledge, becoming a violation of the Health Insurance Portability and Accountability Act (HIPAA). Another important note is the issue surrounding liability. Riddle et al. (2016) mentions that one of the major concerns' anesthesia providers had was regarding an increase in their liability should an adverse event occur even though there was a pharmacogenomics test available. The anesthesia

provider is worried that this exposes them to more liability situations because having all of this increased knowledge could theoretically remove the prospect of human error.

Kaye et al. (2018), Shahandeh et al. (2016) and Mira (2016) all reference reimbursement as another hot topic that needs to be discussed and explained. Kaye et al. and Mira (2016) reference the lack of clarification in regard to where the subsidy for such testing will originate. Initially, there was mention of Medicare and/or Medicaid covering the costs of pharmacogenomics testing for specific types of patients. However, Mira (2016) mentions in the letter that this has now been rescinded and neither entity will be covering pharmacogenomics testing at this time. Shahandeh et al. (2016) conveys both the financial and ethical controversies facing pharmacogenomics testing. The 2016 article references all the different companies available to process such tests, their varying price ranges and in-depth analysis of results. Most importantly, Shahandeh et al. (2016) focuses on the ethical ramifications of such testing being available to the public. As an example, a patient receives pharmacogenomic testing and within the results it is revealed that this patient is at risk or certain to develop a certain pathology based on their genetics. This information can be life altering, however does the patient wish to know what their medical future holds? Even more importantly, who will have access to this information? Is this something that insurance companies could have readily available to them and then utilize this information against a patient and deny medical coverage based on the possibility of future ailments? Van der Wouden et al. (2017) brings up one of the most common barriers found to pharmacogenomics, which is the simple understanding of what this testing is and what may be revealed during the process as well as how to best interpret the results yielded.

Knowledge Deficit

Heale et al. (2017) discovered during their research that there is a significant knowledge deficit regarding pharmacogenomics testing among anesthesia providers, this particular study focused on physician anesthesiologists. When confronted with this information the physicians explained that they did not know enough about the test and more importantly how to properly interpret its results. The physicians demonstrated information-seeking behavior in order to attempt to better understand what this testing was and what it could offer in terms of a more tailored anesthetic. Riddle et al. (2016) conducted a similar study focusing on both physician anesthesiologists and certified registered nurse anesthesiologists (CRNAs). The results were comparable. The overwhelming consensus was that there is a significant lack in knowledge regarding pharmacogenomics testing, and for this reason most of the providers were hesitant to incorporate this into their practice. However, these studies also found that the providers were open to the possibility that this type of testing could ameliorate anesthesia care by providing a tailored anesthetic.

Proactive vs. Reactive

In anesthetic practice, providers are often faced with reacting to the signs, symptoms and physiologic alterations of patients in the peri-operative period. Most interventions are a reaction to events, for instance post-operative nausea and vomiting (PONV), malignant hyperthermia (MH), pseudocholinesterase deficiency and more frequently alterations in vital signs and pain management. All of these factors are reacted to by the anesthesia provider, mostly to treat and intervene after an event has already occurred. Providers are then endeavoring to keep up with and prevent further signs and symptoms of adverse reactions. These topics are discussed at length in articles by Kaye et al. (2018) and Ama et al. (2010). They describe how PONV, MH

and pseudocholinesterase deficiencies play a large role as adverse reactions that affect patients and hospitals. These reactions prolong recovery, delay transfer, and elevate the morbidity and mortality of an often-unexpected response to a typically administered anesthetic regimen. They mention how a majority of the time; providers are unaware of a patient's predisposition to these events until the physiologic process has already begun. Making room for statements that question the lack of utilizing new technologies available to providers to better identify patients at risk, prior to exposing them to potentially dangerous and possible life-threatening adverse reactions. Pharmacogenomics could play a large role in identifying patients at risk for developing any of the aforementioned reactions. Candiotti et al. (2009) focuses on PONV in particular and the role that pharmacogenomics testing could play in recognizing a patient's predisposition to this phenomenon, as well as the genetic polymorphisms affecting metabolism of typical anti-emetics. These authors also touch upon the notion of innate drug resistance being related to the class of either ultra or slow metabolizers, in regard to the altered metabolism of anti-emetic medications leading to their ineffectiveness. Kiley et al. (2017) infers that the employment of pharmacogenomics for pain management would allow for better patient outcomes and optimal pain control. This postulates that if anesthesia providers were to have access to information regarding a patient's ability to metabolize pain medication, they would be able to prescribe the best medication and dosage to regulate pain from the start. This would be the optimal scenario, as opposed to discovering that pain is not being adequately controlled and requires the trial and error drug approach with increasing doses potentiating an adverse drug reaction such as overdose. This all relates to the suboptimal medication being administered. Having the foresight on how a patient might react to certain medications and their doses would provide invaluable information. This allows the anesthesia professionals to optimize patient care and proactively

treat or prevent pain as well as other ailments instead of constantly reacting to events that could have easily been prevented.

Socio-Economic Community Impact

Shahandeh et al. (2016) touches upon the risks associated with having pharmacogenomics testing results shared with insurance companies. One must examine the possibility of insurance companies exploiting this information to prevent patients from acquiring coverage based upon the results. This could have devastating impacts on healthcare and society if this were to slip through government loopholes, becoming a legalized form of overpricing or denial of insurance.

Alternatively, positive societal impacts important to note are the advancements that pharmacogenomics testing provides to patient care. A decrease in ADR and improved patient outcomes would have a vast impact on hospitals and their surrounding communities. Delivering fewer ADR would lead to a more rapid recovery, which boosts patient turnover, facilitating additional treatment of patients in need. According to Mira (2016), 6.7% of ADR lead to death every year. This is a shocking statistic that needs to be acknowledged and significantly reduced. Hicks et al. (2016) and Riddle et al. (2016) have found that incorporating pharmacogenomics into standard practice would decrease the amount of ADR, reducing the number of undesirable and sentinel events. Marchant et al. (2008) and Riddle et al. (2016) agree that utilizing pharmacogenomics would lead to an improvement in global patient outcomes. Van der Wouden et al. (2017) describes how this technology is already in use in Europe with the PREPARE study and has been proven to decrease ADR by greater than thirty percent. This elaborates on information stating that five percent of hospital re-admissions are directly related to preventable ADR. The authors of this article research the impacts of incorporating pharmacogenomics testing

into medicine and have proclaimed that with PGx testing, a postulated fifty percent avoidance of ADR could be achieved. This means that the use of pharmacogenomics would reduce the risk of having an ADR in half, at the moment a patient arrives at the hospital. Van der Wouden et al. (2017) explain that in Europe, pharmacogenomic testing and the results are already incorporated into electronic health record (EHR) and are stored on a uniform platform which is accessible to all the relevant disciplines across the entirety of Europe. This important piece of information can help answer some of the pressing questions that have been raised concerning how providers would be able to disseminate this information appropriately with all the varying medical disciplines that may be involved in a single patient's care. Europe is already ahead of us in the successful incorporation of this technology and can serve as a point of reference for developing a system here in the United States.

Cost Analysis

Ama et al. (2010) defined the yearly cost of ADR to amount to $136 billion. Kaye et al. (2018) elaborates regarding facts of chronic pain generating $600 billion worth of medical costs annually, all directly related to analgesic pain medication prescriptions. This is billions of dollars in healthcare costs that could be vastly reduced with the integration of pharmacogenomics.

Mira (2016) explains a situation where a doctor incorporated information from a patient's pharmacogenomics testing results into the treatment of their chronic pain. This patient was a chronic pain sufferer that reported a constant 10 out of 10 pain which doctors were unable to alleviate for years. This doctor interpreted the pharmacogenomic results and instituted a tailored multi-modal medication plan for this patient. The patient immediately reported a decline in pain levels from the original 10/10 to a more acceptable 4/10 on the pain scale. This demonstrates the fact that utilizing the science and technology available to us can allow for better treatment of

patients and would generate a reduction in the needless expense on ineffective treatments. This could help to greatly reduce the cost that pain management and ADR have on local communities, society and healthcare as a whole. Cohen et al. (2012) explains how they have already incorporated pharmacogenomic testing into multiple facilities and have observed the benefits from this assimilation. They report the cost for the testing is insignificant when compared to the possible cost savings. The cost/benefit ratio is stated to be non-negligible and plays a crucial part in their cost containment of ADR and inappropriate, trial and error, pain management. Van der Wouden et al. (2017) confirms that the increase in favorable outcomes in relation to the use of pharmacogenomics lead to this being a more cost-effective intervention than the current acceptable standard: reaction to an event.

EHR and Prompting

Hicks et al. (2016) and Cohen et al. (2012) explain how pharmacogenomics is already being actively employed by numerous hospitals across the United States and the world. Most of these hospitals have an EHR in place that allows for easy to interpret results and point-of-care prompting of the provider when a particular medication or dose is being ordered. This alerts the prescriber to the patient's individual polymorphisms affecting their metabolic activities and offers the appropriate modifications to deliver the best possible care and outcomes. Kiley et al. (2017) focuses on this technology and its user-friendly characteristics with easy to follow prompts and alerts. They also make it a point to remind the reader that pharmacogenomics is a once in a lifetime test and therefore only needs to be performed a single time to provide this invaluable information for the remainder of the patient's life. Incorporating this information into a universal EHR could prove to be a priceless addition to any patient or provider in the system.

Methodology

This study was a prospective, descriptive, multicohort design which examined the impact of a didactic educational presentation with use of a highly reliable survey set. There were three times and settings where the pre-survey was administered to an educationally diverse group of anesthesia providers followed by the educational presentation. The subsequent post-survey evaluation mimicked the initial survey. This provided statically measurable, qualitative continuous and categorical data as to the efficacy of the educational intervention.

Population

The population of interest to this study were anesthesia providers, specifically physician and nurse anesthesiologists and RRNAs. The anticipated sample size was approximately n=50 anesthesia providers. The actual sample size ended up being n= 60. The variable level of practice the participants had in their different training backgrounds and number of years of experience, provided the investigators with an eclectic population of anesthesia professionals. The participants in the study were all volunteers from an urban academic medical center and a suburban academic medical center in New Jersey. Another group of volunteers that was incorporated into the study were present members of the [redacted] attending the annual conference on October 5, 2019.

Setting

The participants that contributed to this study were found at a large urban academic medical center and a smaller suburban medical center in New Jersey. The facilities that were involved with the implementation of this project are both clinical rotation sites for [redacted] DNP program. Every Monday and Wednesday mornings there are grand rounds respectively at each facility, where the authors presented an educational

supplement on pharmacogenomics to further educate the anesthesia providers. Another location employed to reach anesthesia providers was at the NJANA Fall Symposium on October 5, 2019 in Woodbridge, New Jersey. Although all the data from the providers incorporated in this study was collected in New Jersey, the breadth of the state provided a diverse population of providers from urban, suburban and rural areas of the state and surrounding states.

Inclusion/Exclusion

The candidates that were included are the anesthesiologists, certified registered nurse anesthesiologists and resident registered nurses in anesthesia working in or rotating through these academic medical centers in New Jersey. Participation was open to all providers meeting these criteria on a volunteer basis. The exclusion criteria consisted of non-anesthesia providers and anesthesia assistants as neither were applicable to study findings nor were they available in the survey state, respectively. Those present at any of the three dates of data collection who did not complete either survey completely, and/or have not attended the educational presentation were all excluded.

Consent Procedure

Participation in the study was voluntary and based on the providers willingness to partake. The participants' presence and involvement during the presentation was considered to grant implied consent. Those using personal electronic devices (mobile phones, tablets, etc.) for the surveys were able to view a copy of the online consent (Appendix 6) and agree to participation before completing the survey. Should a participant have wished to have a physical copy, a written consent was made readily available to any and all persons taking the provided paper survey or simply wishing to read a detailed copy (Appendix 7).

Recruitment Strategy

The hospitals chosen to launch this study were a large urban and smaller suburban academic medical facilities with clinical affiliation agreements with Rutgers University. These type of teaching facilities offered participants who are more amenable to engaging in and participating in new academic research studies. The medical centers chosen were locations where the principle investigators have established a certain level of rapport with the anesthesia providers, facilitating enhanced communication. An eye catching, high visibility recruitment flyer was posted in the anesthesia offices of each hospital with all pertinent information required to attend and participate in this research opportunity (Appendix 8).

Ethics

At no point during the study was any identifiable patient or participant information utilized or referenced for any part of the study. All data collected remained anonymous and only utilized for the purposes of this study; they were neither shared nor sold to any outside parties. The primary investigators made the privacy of the participants a priority and adhered to the requirements of the Rutgers University IRB and upheld the standards of the Rutgers University Nurse Anesthesia program to the fullest extent.

Risks and Benefits

There were minimal risks with a study of this nature. One risk affiliated with this study was the potential that the participant anesthesia providers available for the study would be reluctant to participate in full breadth of the research. The primary investigators also risked some providers completely rejecting the concept of incorporating pharmacogenomics into their everyday practices.

An associated benefit with this study was based on the assumption that anesthesia providers would view the incorporation of pharmacogenomics testing into pre-operative evaluations as advantageous and/or necessary to further improve practice. Another benefit of this study is that people would recognize PGx as the future of anesthetic practice and would only become more prevalent in the near future as the need for precision medicine becomes a standard of practice (Kaye et al., 2018).

Project Impact on Policy, Practice, Quality and Healthcare

The project impacted practice by suggesting adoption of PGx into pre-operative testing that would supply the provider with an opportunity for a personalized anesthetic management plan. This project also increased awareness about PGx encouraging anesthesia providers to actively seek out further research on the topic and hopefully pave the way to incorporate PGx into their own future practice. The effect on quality is, simply stated, that it could lead to decreased ADR and improved patient outcomes. Finally, the impact on healthcare would be providing patients with a more tailored anesthetic, subsequently leading to ameliorated patient outcomes and satisfaction. This project expected to alter healthcare policy for the better with a new level of care provided by precision medicine and PGx as a standard to manage patients throughout the peri-operative periods and beyond.

Subject Costs and Compensation

The participants received no form of compensation for their participation in the study. The information was freely distributed at the educational presentations, at no cost to the providers present.

Study Interventions

The participants were provided with a preliminary evaluation of their previous knowledge of pharmacogenomics (Appendix 9). After this, participants were provided with a brief didactic presentation in person about PGx and how to interpret its results (Appendix 10). This was then followed by a post-education evaluation of the providers' receptiveness of pharmacogenomics and conceivable incorporation of PGx into their personal practice (Appendix 11). These surveys allowed the investigators to measure the efficacy of the educational offering and preference of the multimedia method of administration. The demographic data collected was also compared and utilized to identify variables that either promote or hinder the incorporation of pharmacogenomics into practice. The surveys employed for this study have been utilized as a highly reliable derivative of the Ubiquitous Pharmacogenomics Consortium in Europe as described by Just et al. (2017).

Outcomes to be Measured

The outcomes that were measured throughout this study are the providers' willingness to incorporate PGx into their practice. Improved understanding of PGx testing evaluation and potentially stimulated education seeking behavior regarding PGx. Demographic information was also evaluated and allowed the investigators to determine if the age, type, and years of experience of anesthesia providers granted insight to the core of the perceptions and barriers that prevent pharmacogenomics from actively being implemented into routine patient care.

Project Timeline

The timeline (Appendix 5), after IRB approval was granted, for project implementation began on July 12, 2019 (Appendix 6a) with preparation for presentation at a New Jersey urban-academic medical center on July 15, 2019 (Appendix 6b) and a New Jersey sub-urban academic

medical center on July 24, 2019 (Appendix 6c). Final data acquisition culminated at a professional association conference of the [redacted] on October 5, 2019. We evaluated multiple levels of anesthesia providers, ranging from RRNAs, CRNAs and physician anesthesiologist and their responses via questionnaires before and after educational intervention. Analysis of data with Qualtrics statistical software continued from October 6, 2019 to December 9, 2019. The findings were then formally presented after a conclusion to our previously mentioned aims was ascertained at a Final DNP Project Presentation on January 27, 2020.

Resources Needed

A computer, along with Qualtrics interpretative database in order to accumulate, store and analyze the data collected at each of the three events discussed above. Sample PGx profiles were required in order to highlight the information crucial to the anesthesia providers understanding and interpretation of the data provided by various PGx report. A didactic presentation was delivered to the anesthesia providers present at the NJANA Fall Symposium and at two academic medical centers in the heart New Jersey's healthcare consortium.

Evaluation Plan

Description of data collection. Data collection was performed by surveying anesthesia providers that have attended our verbal didactic presentation on pharmacogenomics. The primary goal of the group survey was to educate and evaluate the participants on their perceptions and understanding of pharmacogenomic integration. Qualitative data was collected and analyzed regarding our intervention in order to support or refute our hypothesis.

The data acquired from these 3 locations was kept anonymous. The only personal information required for the study parameters was the demographic information representative of age, years of practice, level of education and type of provider.

Plan for data analysis. The data collected was interpreted by comparing before and after educational intervention results to determine if a change in practice would be embraced by providers in order to benefit the anesthetic care regimen of patients undergoing surgical intervention. Paired *t*-tests was utilized to compare the mean and median results of the surveys in order to identify modification of knowledge base. The data was either directly input by the study participants via online survey administration or manually entered into the Qualtrics data management system by the primary investigators. This system was also utilized to interpret results via statistical analysis and provided the study team with a valuable and relevant product. Multivariate ANCOVA tests were used to determine demographic relation to the expressed receptiveness using both categorical and continuous data points as well as evaluating the efficacy of the method of the intervention.

Data security and storage. The only participant information that was extrapolated was the provider's age, designation, years of experience and highest degree of education. This information was coded for privacy and anonymity via the Qualtrics system. There were no identifiers present to link the information to any participant at any location. All project data was secured onto a password-encrypted file with an ASE-128-bit security encryption on a closed database that was only accessible to the principal investigators.

Anticipated Findings

We suspected that there would be some resistance to the idea of incorporating PGx into pre-operative testing. However, it was believed that there would be a disparity between more

experienced practitioners and more recent graduates. We anticipated that the younger generation of anesthesia providers would be more open and willing to accept the use of PGx into their practice as opposed to long-term practitioners.

Results

The project was implemented in three different settings, and resulted in a total number of 60 participants. Of those participants, 3 failed to complete the post test, thus leaving the investigators with 57 completed pre and post surveys to analyze. Qualtrics software and SPSS were employed in order to run all of the statistical tests. Upon analysis of the data acquired, it was found that there was a clear difference between pre and post surveys scores. After the analysis of the skewness and kurtosis of the data, it was found to be parametric with a normal distribution. A sample paired *t*-test was run on the 57 participants' responses to determine if there was a statistically significant mean difference between the participants' understanding of PGx pre and post intervention. The pre-surveys had a mean of (2.88±1.18) and the post survey resulted in an increased mean of (3.40±1.077). The statistical significance (2-tailed *p* value) was found to be $p=0.009$, where $p<0.05$ with ($t=-2.707$, $df=59$) thereby being statistically significant (Table 1). The Pearson correlation coefficient for the post-test is equal to 1, thereby signifying that the data has a perfect positive association between the educational intervention and the learners' increased understanding of PGx. These results lead to the rejection of the null hypothesis, due to the statistically significant increase of -0.517 (95% CI, -0.899 to -0.135). It can be concluded that an educational intervention regarding the interpretation of PGx could elicit a statistically significant increase in participants' understanding and willingness to employ PGx into their practice.

Table 1. Paired sample *t* test

Paired Differences	Mean		-.517
	Std. Deviation		1.479
	Std. Error Mean		.191
	95% Confidence Interval of the Difference	Lower	-.899
		Upper	-.135
t			-2.707
df			59
Sig. (2-tailed)			.009

When comparing participants' results regarding their perceived familiarity with pharmacogenomics, pre-survey the mean was 2.36 with 27.87% stating that they disagreed and 8.2% who agreed. This parallels with the results of the same question, post intervention, the mean is 3.43 with 0% reporting that they disagreed and 49.06% with agreed (Figure 1). The participants responses regarding their confidence in utilizing pharmacogenomic results to fine-tune their anesthetic plan are laid out in Figure 2. When focusing on the participants' familiarity with interpreting PGx results, 49.18% of the pre-intervention group stated that they disagreed and 0% agreed with a mean of 1.79. Looking at the post intervention responses, 5.66% disagreed, 60.38% somewhat agreed and 26.42% agreed, with a mean of 3.08 (Figure 3).

Figure 1. Survey question responses pre and post intervention (%)

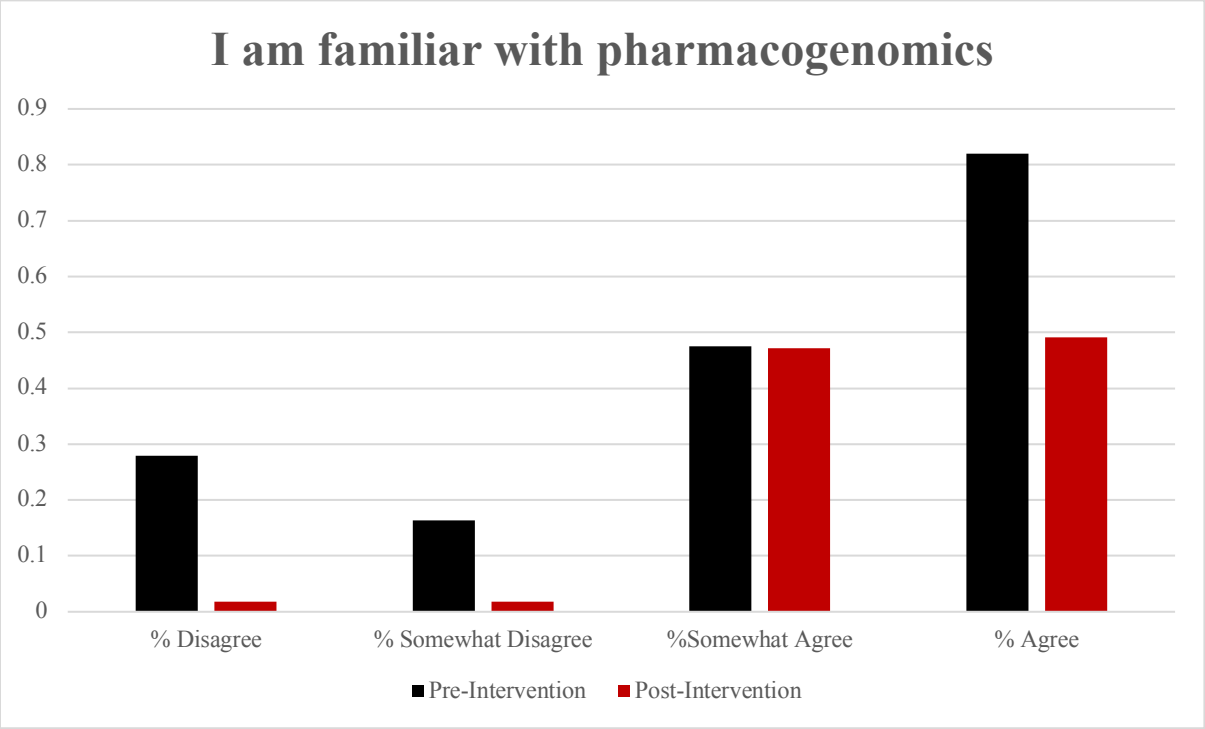


Figure 2. Survey question response pre and post intervention (%)

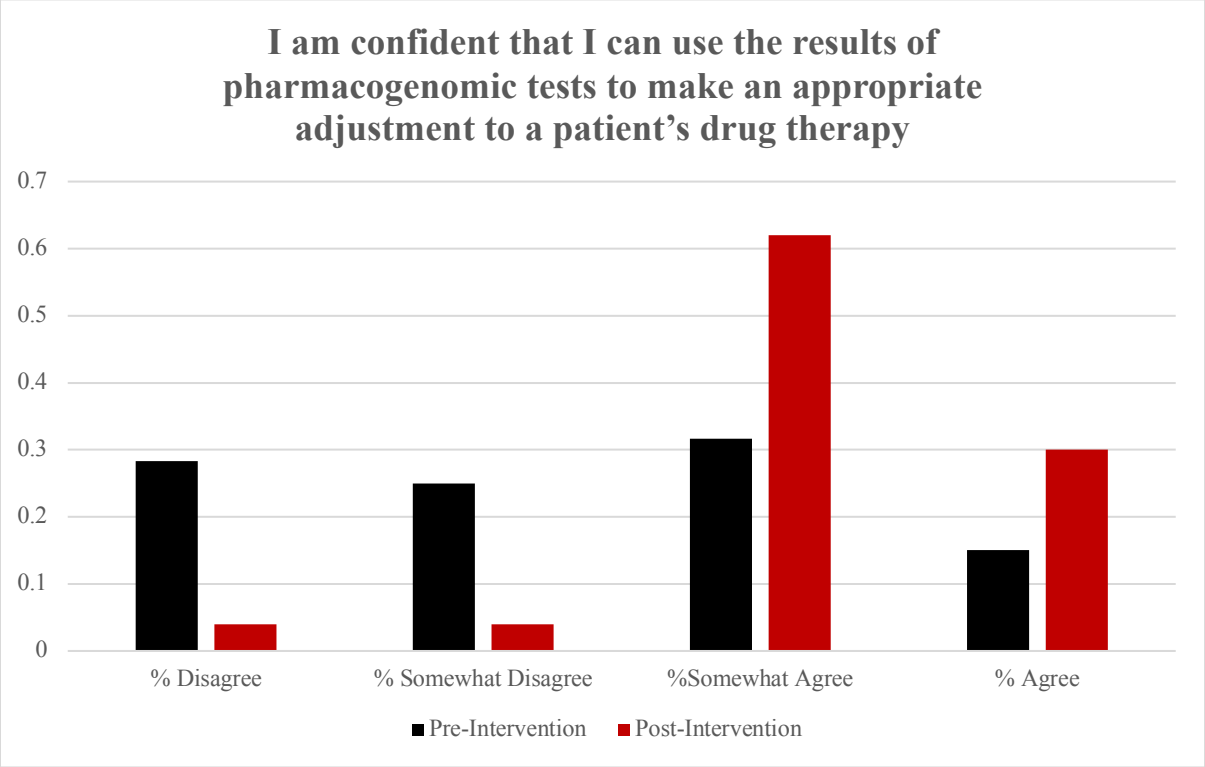
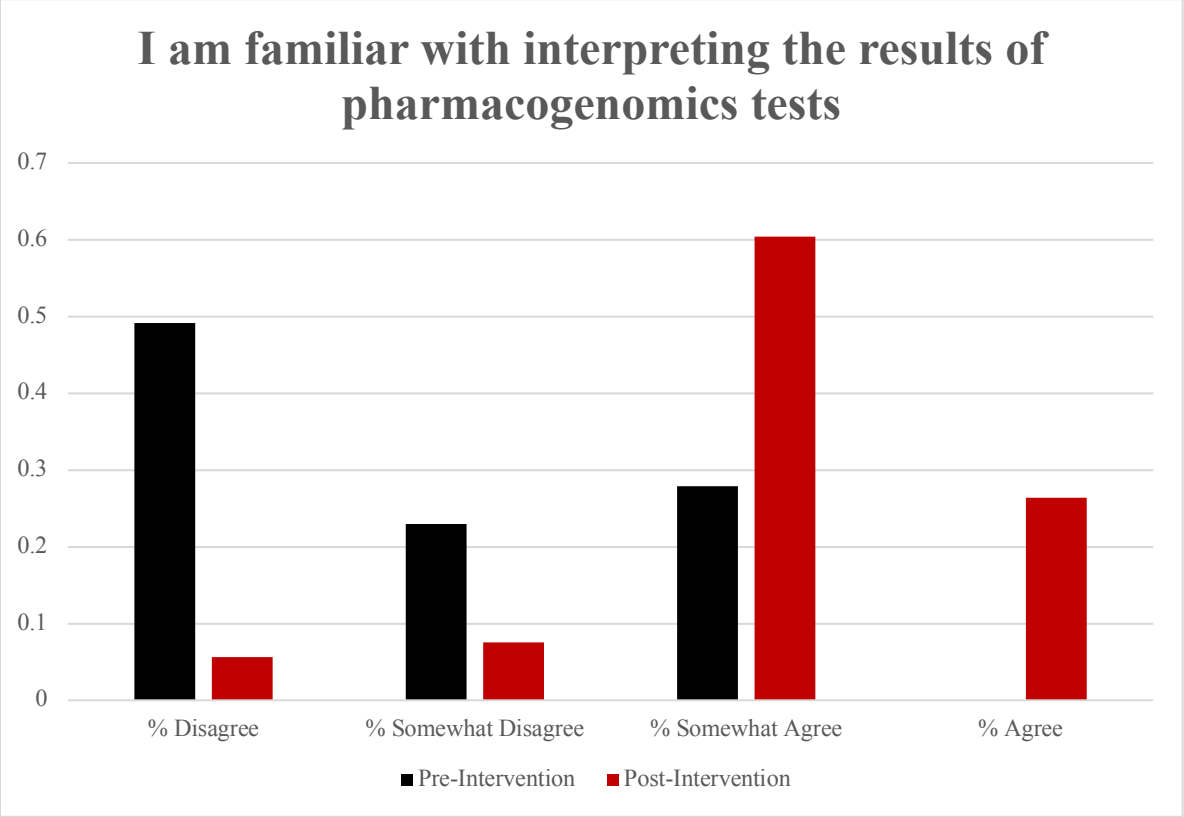


Figure 3. Survey question responses pre and post intervention (%)

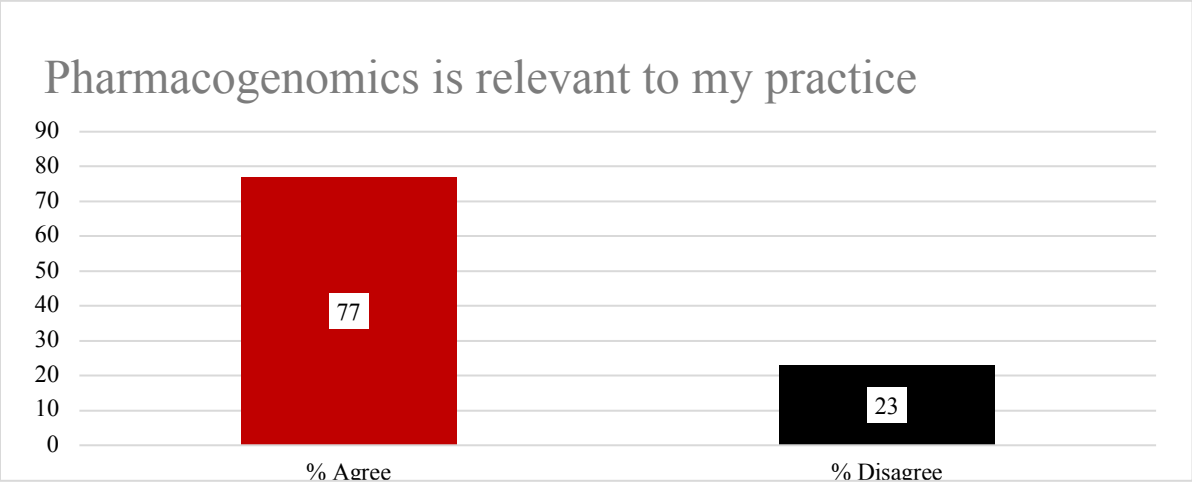


Discussion

Clinical Practice

As evidenced by the results of the project and the participants' feedback, PGx is relevant to most of the anesthesia providers practice and will continue to become more popular. Many of the participants stated that they found this was relevant, and important to learn because they recognize that PGx will only become more prominent in the medical field (Figure 4). Having providers who are educated and comfortable with PGx will lead to better and safer patient care in the future.

Figure 4. Relevance to practice (%)



Healthcare policy

The Center for Disease Control defines healthcare policy as a law based on an innovation that leads to change and ultimately an enhancement in health and healthcare. It goes on to state that healthcare professionals are crucial to this, and their evidence-based research is fundamental to the development of these policies that will better healthcare in the long term (cdc.com, 2015). With the growing popularity of pharmacogenomics testing and the slow integration of its medical interpretation into the standard of practice, this is an area that needs to be highlighted. More and more people are undergoing pharmacogenomics testing, and bringing these tests to their providers. Unless the provider is well-versed in the interpretation of this information, the crucial information on that piece of paper is lost. As discovered before by Riddle et al. (2016) physician anesthesiologists and CRNAs are unfamiliar with the interpretation of this data and are uncomfortable with using this information in their practice. Having healthcare policy keep up with the fast-growing times by recognizing the rise in PGx and advocating for the education on this topic would facilitate its integration into everyday practice. Education is paramount in any advancements in healthcare. PGx is the pinnacle of modern medicine today, and it is imperative

for medical professionals to be well-versed in its interpretation, because it will only grow in popularity and commonality.

Quality and Safety

The FDA reports that there are $136 billion a year lost to ADRs with more than 2 million of them being severe, meaning death, ICU hospitalization and long-term damages (Ama et al., 2010). Newer technology such as PGx offer an invaluable insight into a patient's metabolism and helps the provider predict how they will respond to certain medications. Knowing this information ahead of time could allow for not only safer anesthesia, but better-quality anesthesia. Having the foresight to know that a patient is susceptible to MH without prior history, or pseudocholinesterase deficiency or is a poor/ultra-metabolizer offers instrumental information to the provider. Being aware of a patient's metabolizer status allows for superior and safer pain control in the post-operative period. Understanding a patient's pharmacogenomic profile will permit the anesthesia provider to give the safest and best anesthesia possible for that individual person, thus allowing for a tailored anesthetic.

Education

Education is an important barrier to the incorporation and application of PGx into everyday practice. As discussed previously, one of the main obstacles anesthesia providers have with PGx is a lack of understanding and interpretation of results. The results of this project have also highlighted this need, and has shown that anesthesia providers are open and eager to learn about PGx. This project resulted in positive outcomes, where a brief information session allowed anesthesia providers to gain some understanding on what PGx is and, most importantly, how to translate these results into safe efficient care for the patient.

Medicine is an ever-evolving field, and as providers we need to keep up with the new technologies and practices in order to offer our patients the safest and best care possible. Education plays a big role in medicine by being a cornerstone in patient care. As healthcare providers we automatically become lifelong learners, constantly learning and adapting to the new techniques and technologies.

Economic Implications

As previously discussed, ADRs cost the United States a significant amount of money every year. Hicks et al. (2016) and Riddle et al. (2016) explain that pharmacogenomics could be used to decrease the amount of ADRs and improve overall patient care. This is a test that is run once in a lifetime, and offers precious information about that patient's drug metabolism. Cohen et al. (2012) further explicates that the cost of the pharmacogenomics test is negligible when compared to all of the savings it can help create by preventing ADRs and offering correct medication and dosage administration from the start. Incorporating pharmacogenomics testing into standard practice would save not only hospitals money, but insurance companies, the government and the individuals.

Sustainability and Plans for Future Scholarship

This project confirmed that anesthesia providers are enthusiastic and ready to learn about pharmacogenomics. It also confirms that there is a lack in education regarding the topic of pharmacogenomics and its interpretation. The participants were receptive to the educational intervention presented during this project. Sustainability can be reached by finalizing an educational presentation outlining the specifics of pharmacogenomics and making this easily available to anesthesia providers. Feedback from the participants suggested that they would prefer to learn about pharmacogenomics with a presentation lasting no more than 30 minutes.

Once this presentation is finalized it will be presented to the NJANA and uploaded to their online educational platform, where it will be accessible to CRNAs nationwide wishing to learn about pharmacogenomics. A short survey can be added at the end of the presentation allowing participants to provide feedback in order to best tailor this presentation to optimize everyone's learning.

Conclusion

Throughout this research study the principal investigators have identified a conglomerate of barriers that confront pharmacogenomic integration into medical practice. This fundamental paucity of education and comprehension regarding pharmacogenomics is the foremost theme precluding systemic application of pharmacogenomics into current medical practice. The investigators postulated providing both physician and nurse anesthesiologists with educational material to promote the better understanding of pharmacogenomics and interpretation of its results. Participants were asked to partake in surveys relating to their current knowledge and sentiment towards pharmacogenomics as well as a re-evaluation after the implementation of the educational presentation. The theory was that concise educational supplements would change perceptions of PGx and increase the level of understanding for the participants. This facilitated an increased agreeability to incorporating pharmacogenomics into their current anesthetic practice. The ambition of this study was to promote the eventual assimilation of pharmacogenomics testing and utilization into standard practice. The results concurred with the investigators initial presumptions. The participants expressed a lack of education regarding pharmacogenomics and specifically their desire to learn more about the topic. The more information and confidence providers have on the subject, the better they will be able to interpret

and incorporate it into their practice, which will in turn ameliorate patient outcomes and preserve capital for the ever-expanding healthcare industry.

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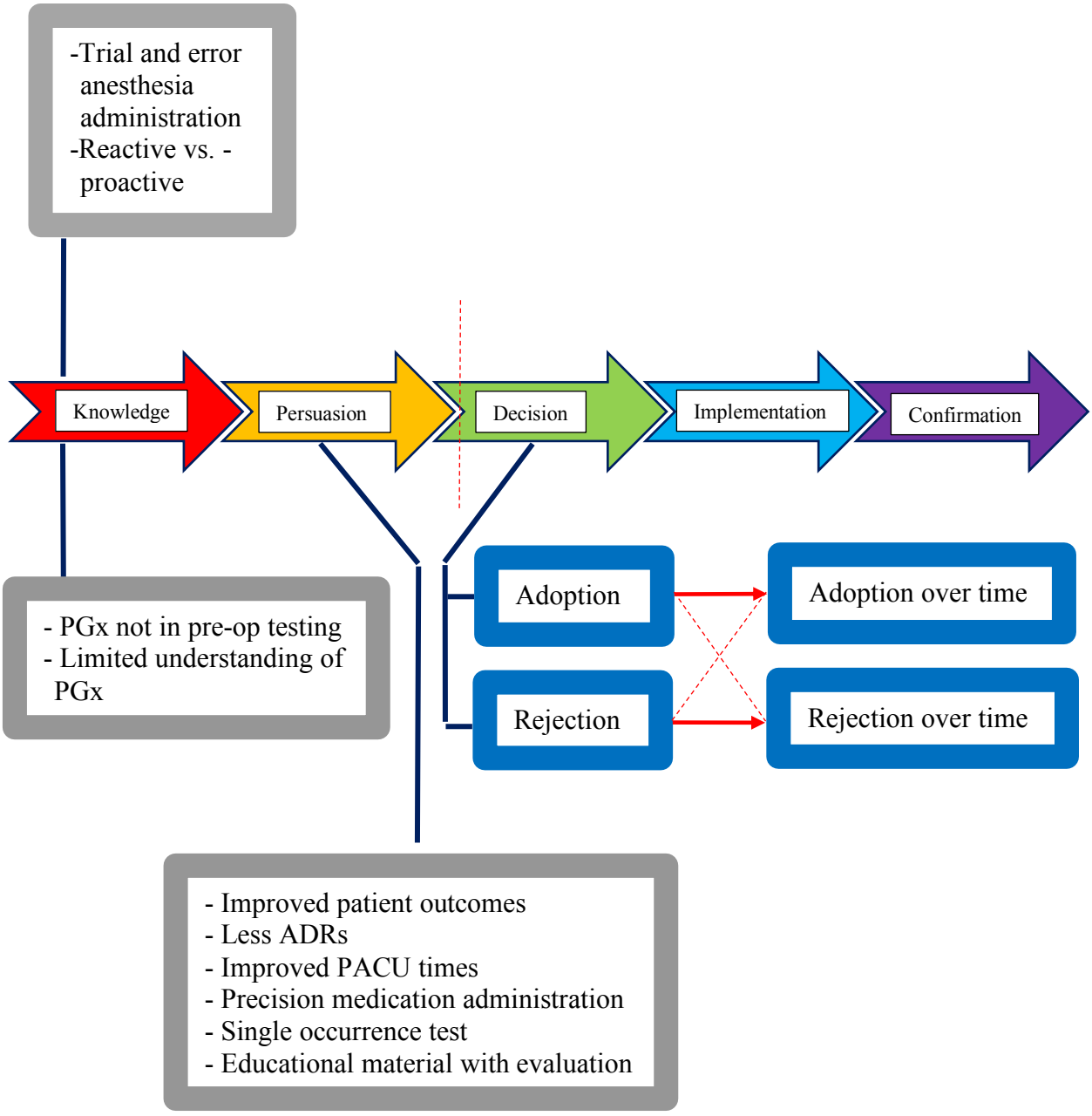
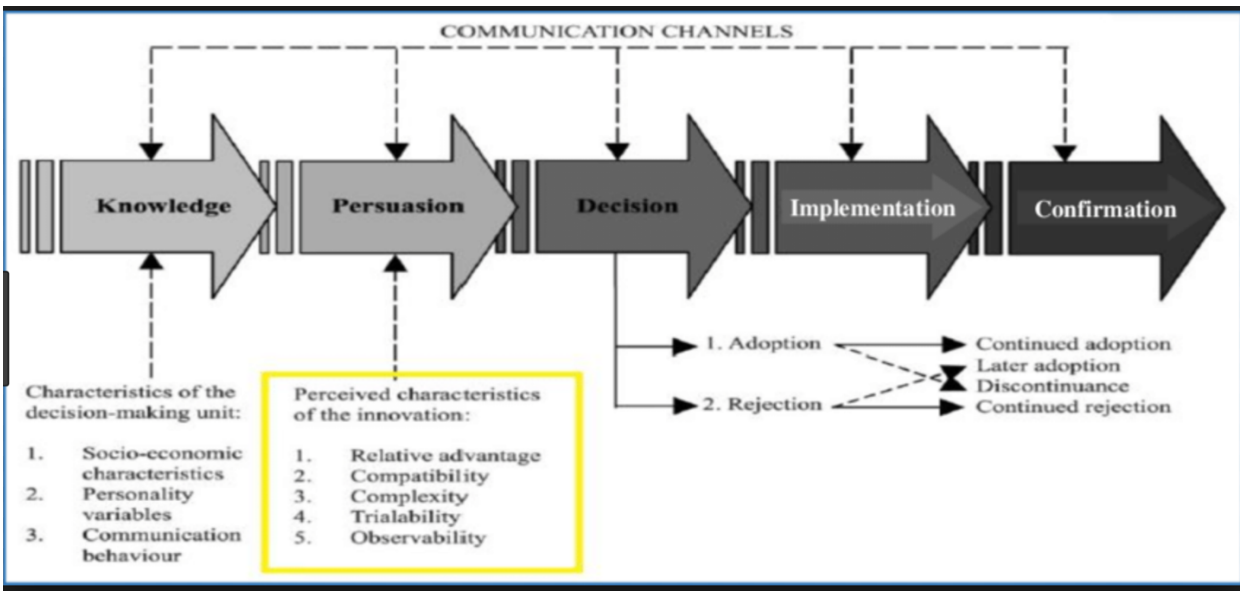
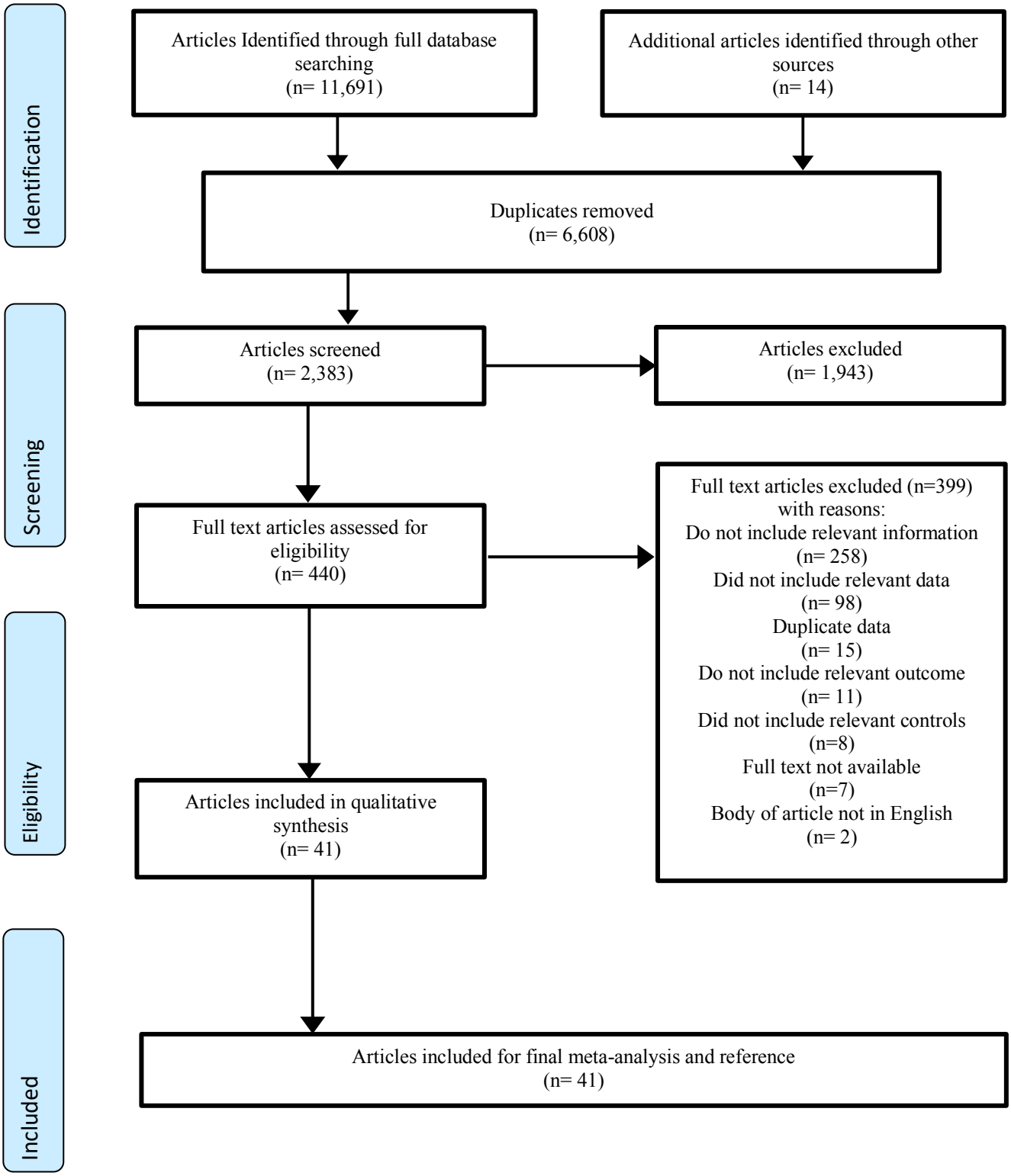
Appendix 1: Roger's Modified Theoretical Framework Diagram



Appendix 2 Roger's Theoretical Framework



Appendix 3: Prisma Table



Appendix 4: Table of Evidence

Article #	Author & Date	Evidence Type	Sample, sample size & Setting	Study findings that help answer the EBP Question	Limitations	Evidence Level of Quality
1	Ama, et al., (2010)	Evidence Based Guideline	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Defines slow metabolizer, intermediate metabolizer and ultra-metabolizer. • ADRs are the fourth leading cause of death in the USA. • ADRs cost $136 billion. • Explain metabolism through CYP2D6. • Explain the impact on metabolism has on pseudocholinesterase deficiency, malignant hyperthermia and PONV.	Educational article however not a study.	IV Good quality
2	Saba, Kaye, & Urman, (2017)	Meta Synthesis	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Explain how more tailored anesthetic would lead to better outcomes and decreased hospital stays. • Explains different particularities within patient's for different medications. • Explains the metabolism of codeine through CYP2D6 into morphine and the effects this has on different patients based on metabolism status (slow vs. ultra).	More of an educational article, does not offer statistical results.	III Good quality

				• Impact each persons' metabolism has on pseudocholinesterase deficiency, MH and PONV.		
3	Shahandeh, et al., (2016)	Evidence Based Guideline	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Discussion regarding the financial and ethical involvements with pharmacogenomic testing. As well as different kinds of genetic testing available. • Microarrays are the most cost effective and fastest way of performing genomic testing. • Microarrays provide high accuracy results. • References the ethical issues of whether a person wishes to know that they are predisposed to some illness, or if the insurance companies can have access to that information and refuse coverage based on the results.	Controversial usefulness of the pharmacogenomics mainly because of the errors in interpreting results.	IV Low Quality
4	Marchant, (2008)	Meta-Analysis	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Explain the importance and role pharmacogenomic testing could have on improving medicine and patient outcomes. • Discusses the political liabilities associated with such technology; like	Discusses the political and privacy barriers associated with a wide spread use of pharmacogenomics.	IV Good quality

				privacy, protection and business laws. • Reimbursement is discussed. • Medicare/Medicaid coverage. • FDA needs to oversee genetic testing to ensure more security.		
5	Chidambaran, et al., (2017)	Evidence Based Guideline	There is no sample for this one, it is focuses on the effects of codeine on different populations, mainly pediatrics	• Explain the wide range of ADRs codeine can have on specific populations and how this can be avoided with the use of genetic testing, thus allowing for more favorable outcomes. • How the interpretation of CYP2D6 variations can affect perioperative pain management. • More study designs are needed.	There needs to be more research done on genotyping for the incorporation into influencing medical practice.	III High quality (possibly II??)
6	Cohen, et al., (2012)	Meta-Analysis	CYP P450 CYP 2D6, 3A4, 3A5, 2B6, 2E1, 2C19	• Explains the importance of genetic testing in improving patient outcomes and how the cost to benefit ratio is not negligible and advocates for its use. • Pharmacogenomics used for perioperative pain management. • Genetic pharmacology already implemented in multiple hospitals around the country.	It is a review of literature of other authors work and not a study of its own.	II High quality

				• Cost of testing is beneficial when compared with the cost savings from avoiding ADRs.		
7	Heale, et al., (2017)	Formative Mixed-method	6 physicians 3pharmacogenomic case vignettes	• Identifies the knowledge gap among physicians regarding pharmacogenomics and its place in medical screening. • Improve patient treatment, reduce costs and ADRs. • Physicians recognize that they are lacking knowledge regarding pharmacogenomics. • Information seeking behaviors. • Physicians question how pharmacogenomics testing would be carried out, who would pay and how long would this test take.	The absence of time constraints on the physicians. Small test group. Prompting towards pharmacogenomic testing.	I Good quality
8	Hicks, et al., (2016)	Meta-Analysis (or meta synthesis)	[redacted]	• Explains the importance of genetic testing to reduce ADRs and advocates for a system that could interpret certain results and prompt the physician with medication/dosage suggestions based off of genetic results. • Multiple different healthcare systems have already incorporated	Funded by the NIH.	IV Good quality

				pharmacogenomics into their practice. • Alert physicians when ordering a medication that this is affected by genetic factors and further testing could be needed. • Provide an easy to interpret table for the results.		
9	Landau, et al., (2012)	Meta-Analysis	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Explains how now there is a definite place for pharmacogenomic testing in relation to cardiac and pain management mediations. • CYP 2D6 and CYP 3A4 metabolism for pain medication.	Not a randomized study.	III Good quality
10	Searle, et al., (2009)	Informational Essay	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• DNA background information. • Pharmacogenetic variations are common however, can make only partial contribution to a patient's drug reaction. • Many of the polymorphisms are point mutations of specific alleles, either insertion or deletion of a base pair. • Single-nucleotide polymorphisms (SNP's) may or may not influence the genetic response to a medication and may lead to a complete loss of response or an	Educational article however not a study.	IV Good Quality

				extremely exaggerated response to a certain medication. • Most current studies investigate the possibility of altered drug responses to an SNP based on current information provided by the Human Genome Project run as case control studies. • It is suspected that the variability in opioid response and reactions are influenced by the SNP's of heterogenicity affecting the PK and PD in varying populations. • SNP's of the Mu1 opioid receptor (A118G) allele occur in 2-40% of the population depending on ethnicity. • One sites study stated that, one SNP alters the binding site and increase affinity and alters signal transmission improving binding of endogenous Beta-endorphins and exogenous opioids. • The homozygous carrier resulted in a 2-4x greater dose of opioids (alfentanil) that was required for pain relief and 10-12x		

				greater dose was needed for respiratory depression. • Though homozygous polymorphisms of A118G increased requirement of IV opioid administration for desired effect, the homozygous patient would also be more sensitive to intrathecal opioids requiring a smaller dose. • Variation in the Beta-arrestin regulatory gene expresses the desensitization of the opioid receptor's s/p prolonged exposure to agonists. Cancer patients would then have a poor tolerance to morphine requiring another opioid for appropriate pain control. • Altered COMT genes can alter the metabolism of neurotransmitters increasing the pain sensation response, hyperalgesia. • This slow metabolism increases endogenous opioid secretion, up-regulating receptors for Mu and causing a smaller dose of opioid to achieve pain control. • In cancer patients, the same polymorphism (p.158VM/VV) were		

				shown to necessitate morphine doses 23%/63% greater for pain management, respectively. • Red-headed women with a MC1R SNP that alters the Kappa opioid receptor function changes response to pentazocine, and also effects this population with a reduced sensitivity to noxious stimuli and increased response to morphine 6-glucuronide. • SNP variations of the P-Gp opioid transporter gene (2677 & 3435) is associated with more serious opioid side effects. • Poor metabolizers (PM's) have two non-functioning alleles • Intermediate metabolizers (IM's) have at least one reduced functioning allele. • Extensive metabolizers (EM's) have at least one well-functioning allele. • Ultra-rapid metabolizers (UM's) have two or more well-functioning alleles. • Caucasian population consists of:		

				PM's – 5-10%, IM's – 10-15%, EM's – 65-80%, UM's – 5-10%. Lowers UM's are from China at 0.5% and Highest in Ethiopia at 29%. • UM administered codeine exhibit a 50% greater amount of morphine compared with EM's. • Tramadol utilization was 30% higher among PM's, requiring a much higher dose to reach a level of pain relief over an EM. • MCR1 gene variant of red headed individuals is responsible for the 19% greater requirement in MAC of Desflurane. • Sevoflurane requirements and ethnicity is another, unidentified area, but known relation. • Nitrous Oxide should not be administered to MTHFR deficiency patients as the incidence of acute demyelination syndrome even after short duration.		
11	Kiley, (2017)	Opinion paper	Not a study	• Right medication at the right time to target opioid need.	Educational article however not a study.	IV Poor Quality

				• Should be incorporated into a EHR. • Alerts during prescription. • PGx is a one-time test for individuals. • Prevention for adverse events before they occur. • Knowledge of the type of metabolizer the patient is then the better the control of pain and greater limit of adverse events related to overdosing or under-dosing.		
12	Candiotti, (2009)	Opinion paper	Not a study	• Limited information of PGx for anesthesia exists and is due to poor trials with limited participants. • Poor trials are related to the increased cost of testing and lack of time for optimal evaluation of the information. • Post-operative nausea and vomiting (PONV) is an example of an area when PGx testing could identify a PM or UM, and the dose of a 5-HT3 medication may not be effective in treating the PONV related to these genetic variations. • There are few genetic trials for PGx therefor the information physicians have to	Educational article however not a study.	IV Poor Quality

				evaluate data is considered inconclusive. • More trials are necessary to properly evaluate the use of PGx in the anesthesia population. • "Genetic drug resistance" could be the reason, for example, standard dosages and regimens of antiemetics are administered to anesthesia patients. • Anesthesia providers provide multimodal therapy for PONV and are already treating some of these genetic variables without complete understanding. • Knowing the exact variant of the gene expression is not necessary, clinicians can easily utilize data from PGx in their practice with the inclusion of with gene the patient may be a PM, EM, or UM.		
13	Riddle, (2014)	Principle-based concept analysis	Information relating to the provider as to the concept of pharmacogenomics and the lack of utilization.	• Use of PGx informs providers to make better clinical decisions for their patients. • Not utilized as study findings are still not specified. • Genetic predisposition is utilized for clinical	Educational article however not a study.	III poor Quality

				decision making, relation of history one family member may have about a disease or condition or the simplified term of pharmacogenetic variability of the effect a drug or class of drug can have on an individual.		
15	Riddle, et al (2016)	Qualitative-quantitative sequential mixed-method	-10 participants in qualitative phase -6000 participants in quantitative phase	• Proves that there is a lack in the education of anesthesia providers regarding pharmacogenomics. • Pharmacogenomics improves satisfaction and decreases ADRs. • Anesthesia providers don't have enough knowledge about pharmacogenomics or the ethical implications. • Pharmacogenomics proved to improve patient outcomes, but not enough studies on its role in decision making. • Anesthesia providers concerned about economic implications and need more information regarding cost-benefit ratios. • Possibility for increased liability and exposure if aware of how drugs affect a particular individual.	All qualitative participants were located in Texas. Small response group from the quantitative could have skewed the results.	III High quality

				• Think that pharmacogenomics is very difficult to understand and grasp. • Agreed that more information would allow to have a more tailored and better anesthetic. • Unaware of the minimal cost of the tests and lack of education regarding pharmacogenomics		
14	van der Wouden, et al., (2017)	Evidence-based guidelines	Informs the reader about implementation, background and many other questions associated with pharmacogenomics.	• PGx skips the trial and error of medication administration. • PGx is used for "Personalized medicine" an area that promises better ailment and symptom control with fewer side effects, adverse reactions or set-backs in care regimens. • More effective and cost-effective treatment with PGx. • Significant barriers are physician and pharmacist understanding of PGx. • There are multiple healthcare organizations testing the use of PGx and incorporation into their patients EHR's to provide point-of-care prescribing information to providers in order to	Educational article however not a study.	IV Good Quality

				prevent ADR's and limit other variables of medication dosing. • Ubiquitous pharmacogenomics consortium (U-PGx) instituted QR code data transfer that can be scanned by pharmacists and physicians to assure appropriate medication prescribing, in Europe. • Provider and patient education are important for the appropriate use of PGx. • The PREPARE study of PGx implementation is thought to provide a 30% or greater decrease in ADR's. • Use of the European "Safety-code" card makes information easily accessible for providers and interpret the PGx information to guide therapy. • Dutch Pharmacists Working Group (DPWG) guides PGx implementation guidelines for patient and physician use to assure data is uniform and able to be utilized in multiple areas of Europe. • DPWG states 50 variants of 13 paired		

				genes be used for initial phenotyping to discover clinically relevant variables. • Up to 50% of ADR's could be avoided with PGx. • 5% of hospital admissions are related to ADR's.		
16	Mira, (2016)	Meta synthesis (A letter) Expert opinion	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Explains the role pharmacogenomics has in the future of anesthesia and medicine. Discusses the road blocks and how they may be overcome. • Tailored anesthetic would lower ADRs and extended hospital stays. • Using knowledge of risk of opioid dependence to provide opioid free anesthesia. • 6.7% of hospitalized patients have ADRs some leading to death	This is simply a reiteration of previous information and not a study of its own.	V High quality
17	Kaye, et al., 2018	Meta-synthesis	There is no sample for this one, it is more of a background article explaining what pharmacogenomics is and what studies	• Earliest report in 510BC with fava beans causing hemolytic anemia. • Multiple approaches to PGx: 1. Small number of genes studied. 2. Larger with genome-wide associations of studied. 3. Exomes and Genomes are studied, and variants are identified.	This is simply a reiteration of previous information and not a study of its own.	V Good Quality

				• Precision medicine considers individual patient reactions of the PK of drugs. • Anesthesiology is linked closely to PGx. • PGx will be at the forefront of precision medicine. • Human Genome Project categorized 60,000 single-nucleotide polymorphisms [SNP]-trait associations in more than 3300 studies. • Significant considerations for implementation of PGx in the pre-operative setting: 1. Clinical science. 2. Socioeconomics. 3. Computer technology. • Common peri-operative agents with PGx biomarkers: 1. Codeine, tramadol, ondansetron & metoprolol – CYP-2D6. 2. Lidocaine – G6PD. 3. Succinylcholine – BCHE. 4. Metoclopramide – G6PD & CYB5R. • EHR necessitates large storage requirements for approximately 40 exabytes of data. • Should only have clinically relevant		

				biomarkers recorded to optimize storage. • Lack of strong evidence of usefulness limits reimbursement for PGx testing. • Need more evidence for improved patient outcomes before insurance companies will realize cost-savings. • In 1956 Succinylcholine was released and within a year tests were performed to assess why some patients had prolonged periods of apnea. Dibucaine Number was released and is still gold standard after reaction has occurred. • Caffeine-Halothane test for MH is gold standard since 1970, however, in 1990 the ryanodine RYR1 gene variant was identified and can be tested for with PGx testing. • Phase 1 metabolism of drugs is heavily CYP-450 dependent. Nearly 80% of drugs metabolized by CYP-1,2 or 3. • CYP-450 variants are linked to ethnicity. • 7% of Caucasians and African Americans have a		

				functionally silent CYP-2D6 enzymatic system, altering metabolism of a significant number of drugs. • Warfarin affected by the CYP-2D6 and VRORC1 genomes relate to the fact that Asians require small doses than Caucasians. • Low levels of BCHE or pseudocholinesterase cause prolonged effects of Succinylcholine and local anesthetics contributing to prolonged apnea up to 8 hours after standard dose or local anesthetic toxicity, respectively. • 93% of MH patients exhibit the RYR1 gene variant in patients with central core disease. • Four types of metabolizers: 1. Poor, 2. Intermediate, 3. Extensive & 4. Ultra-rapid. • Poor metabolizers when administered analgesic prodrugs like codeine or tramadol have little to no effect. • Ultra-rapid metabolizers when administered the same normal dose of		

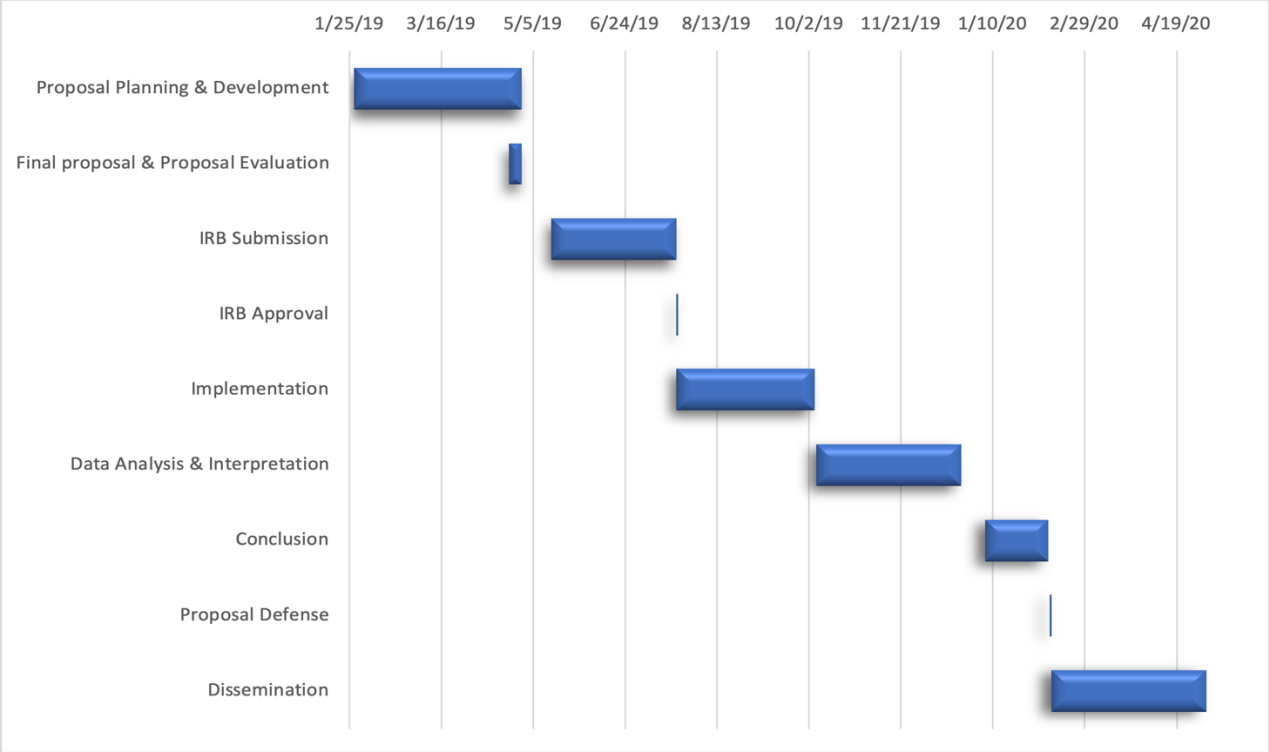
				codeine or tramadol, could have significant adverse reactions such as respiratory depression. • Analgesics that rely on CYP-2D6 such as Tramadol, Hydrocodone and Oxycodone should not be administered to patients who are poor or ultra-rapid metabolizers and alternative non-opioids should be utilized. • CYP-2D6 polymorphisms vary with ethnicity; Ethiopian, Arab, and North African individuals have been shown to have nearly a 30% prevalence rate for the ultra-rapid metabolizer genotypes. • A 45% prevalence of poor functioning CYP-2D6 occurs in east Asian populations and 35% or African-American compared to only 7% of Caucasians. • Rocuronium genome variants of SLCO1B1 and ABCB1, both hepatobiliary genes responsible for elimination of rocuronium, showed significant increased duration of action.		

				• Red-heads with a MC1R polymorphism have a 16% increased MAC requirement for Desflurane. • In 2013, chronic pain produced $600 billion of the medical costs related to analgesic medication prescriptions. Because response to pain medications is not uniform and equivalent dosages can either be harmful for some patients or not provide pain relief for others. This guessing game costs time and money. • A substitution of adenine for guanine on the Mu OPRM1 receptor gene A118G can produce increased affinity and binding of beta-endorphins increasing the effect of some opioids and producing higher instances of dependence behaviors. • Specifically, OPRD1 polymorphism in the African-American population are linked to cocaine addiction. • Morphine is transported across the Blood brain barrier by P-glycoprotein which is encoded by		

				ABCB1 gene, variants of this gene can increase rapidity of transport significantly lengthening admission times relating to adverse effects on the respiratory center of the brain. • Fentanyl administration in patients with a polymorphism of the CGRP gene had worse pain control, required significantly higher doses of fentanyl and experienced little to no nausea/vomiting related to administration. • "One size fits all" is not a viable method of patient treatment at this time of technological advancements. • Precision or tailored medicine is not just for cancer patients, it is for all practitioners looking for a safer method in delivering anesthesia. • In the future, precision medicine is another avenue for safer and more accurate medication administration that will be able to circumvent the adverse reactions and		

				side effects that plagues patients every day.		

Appendix 5 – Gantt Chart Timeline



Timeline of Events			DURATION (days)
START DATE	END DATE	DESCRIPTION	
1/28/19	4/29/19	Proposal Planning & Development	91
4/22/19	4/29/19	Final proposal & Proposal Evaluation	7
5/15/19	7/22/19	IRB Submission	68
7/22/19	7/22/19	IRB Approval	1
7/22/19	10/5/19	Implementation	75
10/6/19	12/24/19	Data Analysis & Interpretation	79
1/6/20	2/9/20	Conclusion	34
2/10/20	2/10/20	Proposal Defense	1
2/11/20	5/5/20	Dissemination	84

Appendix 7 – Anonymous Online Consent Form

RUTGERS

Rutgers School of Nursing
Stanley S. Bergen Building
Rutgers, The State University of New Jersey
65 Bergen Street
Newark, NJ 07101-1709

CONSENT TO TAKE PART IN A RESEARCH STUDY

TITLE OF STUDY: Deciphering Pharmacogenomic Implications for the Anesthesia Provider
Principal Investigator: Thomas Pallaria DNP, CRNA, APN/A
Co-Investigators: Michael D. Daley RN, BSN & Julie S. Greenberg RN, BSN

This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not. After all of your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You will be given a copy of the signed form to keep. Your alternative to taking part in the research is not to take part in it.

Who is conducting this research study and what is it about?
You are being asked to take part in research conducted by Michael and Julie who are nurse anesthesia residents in the School of Nursing. The purpose of this study is to evaluate and educate the anesthesia providers on the utilization of pharmacogenomics.

What will I be asked to do if I take part?
The pre-survey regarding current views and knowledge of pharmacogenomics will take about 5 minutes to complete. There will be a 20-minute educational presentation on appreciation and interpretation of pharmacogenomics for anesthesia providers. The post-survey regarding enhanced understanding and interpretation of pharmacogenomics will take 5 minutes to complete. We anticipate 125 subjects will take part in the study for a total time requirement of 30 minutes.

How will information about me be kept private or confidential?
All efforts will be made to keep your responses confidential, but total confidentiality cannot be guaranteed. No identifying information will be collected or distributed.
We will use Qualtrics to collect and forward your anonymous responses to us. We will not receive any information that can identify you or other subjects. We will download your responses to a secure file that requires a password to access. Only study staff will have access to the password. Responses will be deleted from the file May 2020 after analysis is complete and study findings are professionally presented or published.

No information that can identify you will appear in any professional presentation or publication.

What will happen to information I provide in the research after the study is over?

The information collected about you for this research will not be used by or distributed to investigators for other research. Your participation is voluntary. If you choose to take part now, you may change your mind and withdraw later. If you do not click on the 'submit' button after completing the form, your responses will not be recorded.

Who can I call if I have questions?
If you have questions about taking part in this study, you can contact the Principal Investigator: Michael D. Daley at [redacted] or Julie S. Greenberg at [redacted]. You can also contact my faculty advisor Dr. Maureen McCartney CRNA, DNP, APN [redacted]. If you have questions about your rights as a research subject, you can call the IRB Director at: Newark HealthSci (973)-972-3608.

Please print out this consent form if you would like a copy of it for your files.

By beginning this research, I acknowledge that I am 18 years of age or older and have read and understand the information. I agree to take part in the research, with the knowledge that I am free to withdraw my participation in the research without penalty.

Click on the "Next" button to confirm your agreement to take part in the research.

[redacted]

Appendix 8 – In-person Consent Form

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65 Bergen Street
Newark, NJ 07101-1709

IMPLIED CONSENT TO TAKE PART IN A RESEARCH STUDY

TITLE OF STUDY: Deciphering Pharmacogenomic Implications for the Anesthesia Provider
Principal Investigator: Thomas Pallaria DNP, CRNA, APN/A
Co-Investigators: Michael D. Daley RN, BSN & Julie S. Greenberg RN, BSN

This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not. After all of your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You will be given a copy of the signed form to keep. Your alternative to taking part in the research is not to take part in it.

Who is conducting this research study and what is it about?
You are being asked to take part in research conducted by Michael and Julie who are nurse anesthesia residents in the School of Nursing. The purpose of this study is to evaluate and educate the anesthesia providers on the utilization of pharmacogenomics.

What will I be asked to do if I take part?
The pre-survey regarding current views and knowledge of pharmacogenomics will take about 5 minutes to complete. There will be a 20-minute educational presentation on appreciation and interpretation of pharmacogenomics for anesthesia providers. The post-survey regarding enhanced understanding and interpretation of pharmacogenomics will take 5 minutes to complete. We anticipate 125 subjects will take part in the study for a total time requirement of 30 minutes.

How will information about me be kept private or confidential?
All efforts will be made to keep your responses confidential, but total confidentiality cannot be guaranteed. No identifying information will be collected or distributed.
We will use Qualtrics to collect and forward your anonymous responses to us. We will not receive any information that can identify you or other subjects. We will download your responses to a secure file that requires a password to access. Only study staff will have access to the password. Responses will be deleted from the file May 2020 after analysis is complete and study findings are professionally presented or published.

No information that can identify you will appear in any professional presentation or publication.

What will happen to information I provide in the research after the study is over?

The information collected about you for this research will not be used by or distributed to investigators for other research. Your participation is voluntary. If you choose to take part now, you may change your mind and withdraw later. If you do not click on the 'submit' button after completing the form, your responses will not be recorded.

Who can I call if I have questions?
If you have questions about taking part in this study, you can contact the Principal Investigator: Michael D. Daley at [redacted] or Julie S. Greenberg at [redacted]. You can also contact my faculty advisor Dr. Maureen McCartney CRNA, DNP, APN [redacted]. If you have questions about your rights as a research subject, you can call the IRB Director at: Newark Health Sciences (973)-972-3608.

Please print out this consent form if you would like a copy of it for your files.

By beginning this research, I acknowledge that I am 18 years of age or older and have read and understand the information. I agree to take part in the research, with the knowledge that I am free to withdraw my participation in the research without penalty.

Your consent to participate in this study is implied and confirmed by completion of all activities involved with this study.

[redacted]

Appendix 9 – Recruitment Flyer

Invitation to Participate in a Research Study

We are looking for anesthesia providers currently practicing in the acute care setting for an educational opportunity on pharmacogenomics.

Research Study:
Regarding the utilization, barriers and benefits of pharmacogenomics in the practice of anesthesia.

Educational opportunities will be held at:

1. [redacted] during anesthesia grand rounds on Monday, July 15, 2019 at 0700.
2. [redacted] during anesthesia grand rounds on July 24, 2019 at 0700.
3. [redacted] on October 5, 2019.

Purpose & Activities for Participants:

- Document and evaluate the providers perception of pharmacogenomics and the barriers facing implementation. (5 min survey)
- Educate providers on the analysis of data and potential necessity of pharmacogenomics in the future through interactive presentation. (20 min)
- Re-evaluate for potential changes in perception relating to pharmacogenomics. (5min survey)

Pharmacogenomics

Please help by participating in a study that examines the barriers to implementing pharmacogenomics into practice. Information of accessing and interpretation of pharmacogenomics reports is also available for those who complete a short pre/post evaluation.

Pharmacogenomics is on the horizon to create a safer future for our patients. Be on the forefront of change and let us know what you think.

CONTACT INFORMATION:
THOMAS PALLARIA DNP, CRNA, APN/A - PRIMARY INVESTIGATOR
MICHAEL D. DALEY SRNA - [redacted]
JULIE GREENBERG SRNA - [redacted]

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[redacted]

Appendix 10 – Pre-Educational Survey

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Deciphering Pharmacogenomic Implications for the Anesthesia Provider Pre-intervention survey

Unique Numerical Identifier (This will be the same number as for post-test to compare data):
_____

Section 1: Experience and Attitude

1. Please rank.
   Pharmacogenomics is relevant to my current practice.
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

2. In general, on which of the following do you predominantly base your drug dosing? (select all that apply)
   - Body weight
   - Renal function
   - Liver function
   - Age
   - Pharmacogenomics
   - Comorbidities
   - Comedication
   - Other:
     _____

Section 2: Knowledge

3. Please rank your perceived knowledge on a scale.
   I am familiar with pharmacogenomics.
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

4. Where did you learn about this topic?
   - University
   - As a junior staff member
   - Conference
   - Journal
   - Internet
   - Never
   - Other:
     _____

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5. Please rank your perceived knowledge on a scale.
   I am familiar with the role of drug metabolizer phenotypes (e.g. a poor metabolizer).
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

6. Please rank your perceived knowledge on a scale.
   I am familiar with interpreting the results of pharmacogenomics tests.
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

7. Where did you learn about this topic?
   - University
   - As a junior staff member
   - Conference
   - Journal
   - Internet
   - Never
   - Other: _____

Section 3: Knowledge Testing

Please answer the following questions to the best of your knowledge (select one answer only per question).

8. What may be the consequence of a pharmacogenomic polymorphism?
   - An individual cannot metabolize any drugs
   - An individual has a higher risk for toxicity when using prescription drugs
   - A single drug dose is appropriate for a given indication
   - Individualized dose adjustments should be made according to body surface area

9. What does a poor metabolizer (PM) phenotype indicate?
   - Lower drug safety because of poor metabolism
   - Good drug efficacy because of poor metabolism
   - Decreased enzyme activity
   - Increased enzyme activity

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10. A person who is a PM for CYP-2D6 gets a medication that induces CYP-2D6. That may be a consequence?
    - Decreased CYP-2D6 activity
    - No activity of CYP-2D6, no consequence
    - Increased CYP-2D6 activity
    - The person becomes an intermediate metabolizer (IM) for CYP-2D6

11. Please rank your perceived knowledge on a scale.
    I am confident that I can use the results of pharmacogenomic tests to make an appropriate adjustment to a patient's drug therapy.
    - 1 Disagree
    - 2
    - 3
    - 4 Agree

12. To adjust therapy based on pharmacogenomic tests (more often) I would need… (select all that apply)
    - Better knowledge on pharmacology
    - Better knowledge of pharmacogenomics
    - Better knowledge of legal regulations
    - Insurance coverage
    - Other:

      _____

13. What is your current age? _____

14. What is your title / profession?
    - SRNA
    - CRNA
    - MD/DO
    - Other:

      _____

15. What is your highest level of education completed?
    - BSN
    - Diploma
    - MSN
    - DNP
    - MD/DO
    - PhD

16. Number of years of anesthetic practice?
    - < 1
    - 1-2
    - 3-5
    - 6-10

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- 11-15
- >15

17. Please list any additional comments or feedback here:

Thank you for your participation in our study,

Michael D. Daley and Julie S. Greenberg

[redacted]

Appendix 11 – Educational Adjunct

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Demystifying Pharmacogenomics for the Anesthesia Provider

Michael D. Daley, BSN, RN, CCRN, SRNA
Julie S. Greenberg, BSN, RN, CCRN, SRNA
DNP Chair: Thomas Pallaria, DNP, CRNA, APN
DNP Team Member: Maureen McCartney-Anderson, DNP, CRNA, APN

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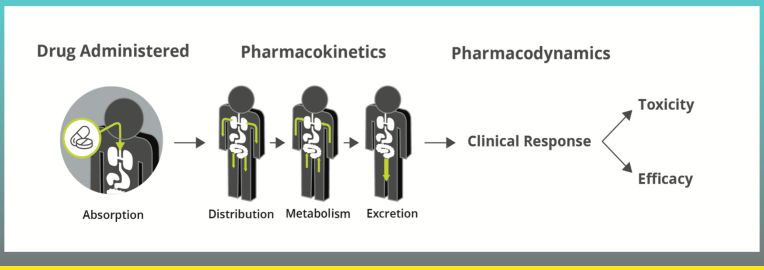
https://tinyurl.com/pgxpretest1

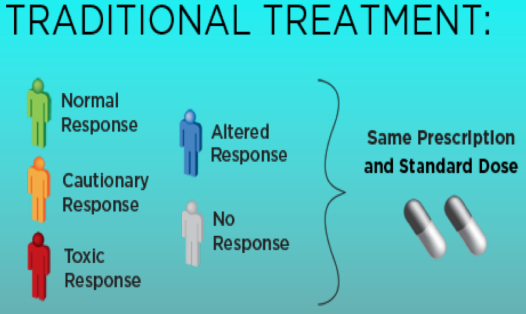
Introduction

- Pharmacogenomics is the analysis of genes and how they affect an individual's reaction to medications.
- Every person's reaction to medications is based on their genomic profile.
- Pharmacogenomic testing is a once in a lifetime non-invasive test.

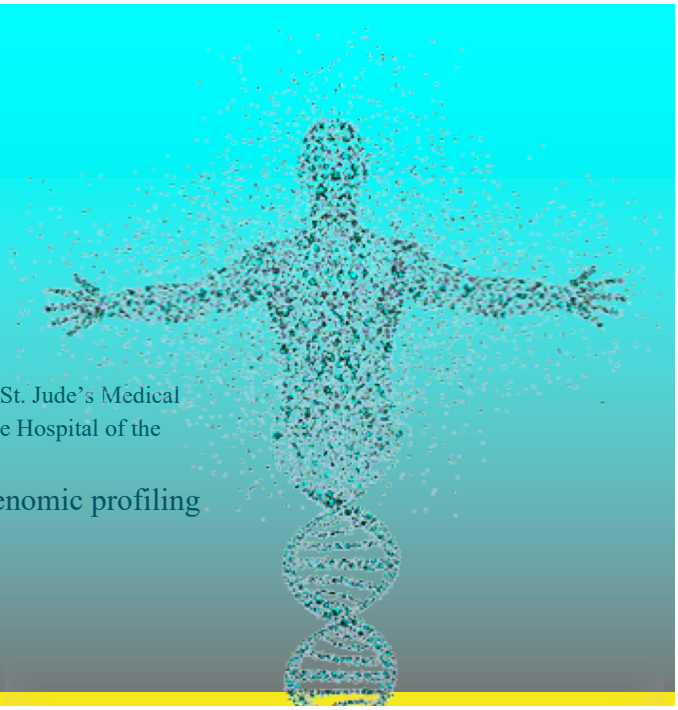


Definition

- What are pharmacogenomic (PGx) polymorphisms?
  - PGx polymorphisms can take many forms
  - It explains how a person metabolizes medications based on their genome
  - There are three main types of polymorphisms
    - Poor/slow
    - Intermediate
    - Ultra/ rapid
  - Based on the type of polymorphism the patient will have varying responses to medications will ensue.



Background

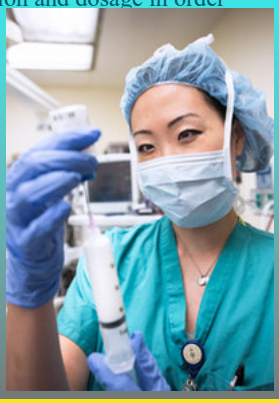


Currently being used:

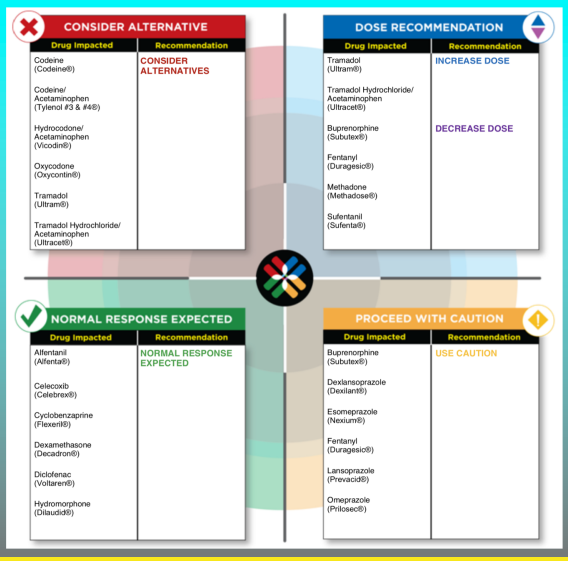
- All across Europe
- In the USA at:
  - Mayo Clinic, Boston Children's Hospital, St. Jude's Medical Center, Mount Sinai Medical Center & The Hospital of the University of Pennsylvania, etc.
- All on the cutting edge of pharmacogenomic profiling for enhancing patient outcomes.

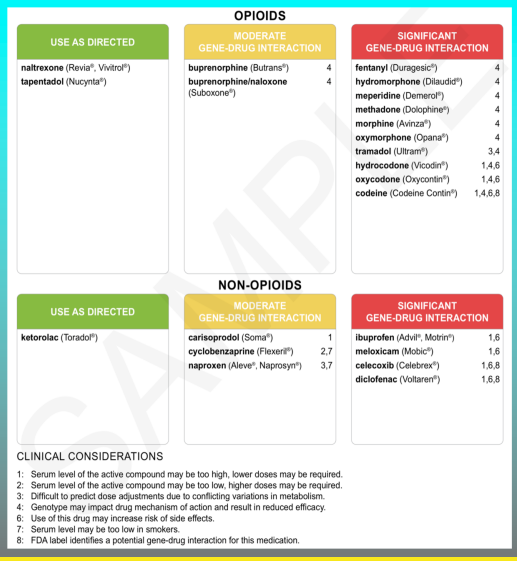
Why is PGx important for anesthesia providers?

- **The impact on pain management:**
  - Knowing a patient's polymorphism helps the provider identify the right medication and dosage in order to provide optimal pain relief
  - Increased success with pain management and patient safety
- **Impact ADRs have on Healthcare:**
  - According to the FDA ADRs cost $136 billion a year
    - Causing increased PACU stays, hospital admissions
    - 1 in 5 patients will suffer harm or death from ADRs
- **Case Study with breast-feeding mother and infant overdose.**



Sample PGx report



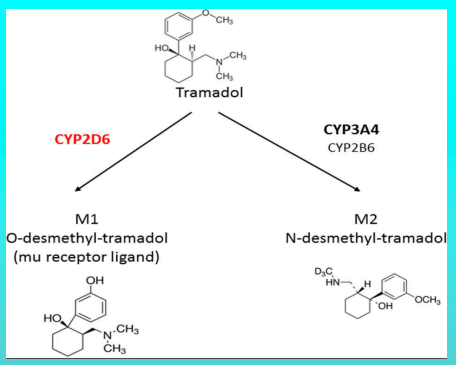


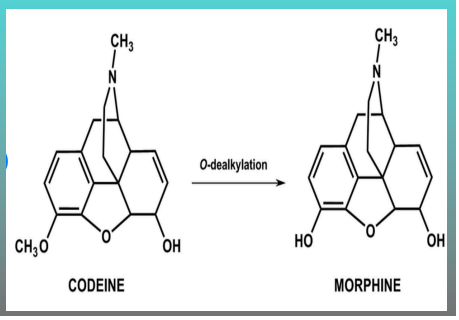
Interpretation and Implications

	Poor Metabolizer	Intermediate Metabolizer	Ultra Metabolizer
CYP2D6 (ie. Ondansetron)	Decreased metabolism of drug, higher plasma drug concentration	Anticipated response	Increased metabolism, shorter duration of action
Dose adjustments	Decreased dose	No dose adjustments needed	Increased dose

Prodrugs and PGx

	Poor Metabolizer	Ultra Metabolizer
Codeine/Tramadol	Lack of pain relief, unable to properly metabolize prodrug into active drug - Decreased efficacy	Increased risk of side effects from fast metabolism into active drug - Toxicity





Anesthesia Medication Breakdown – Narcotics

Medication	Gene Affected	Functional Variant	Effect of Polymorphisms
Morphine	UGT2B7, CYP2D6, COMT, OPRM1	CYP2D6*A; rs1045642*A, rs4680*A, SLC22A1*3	Ultra CYP2D6*A & rs1045642*A: decreased dose in woman. rs4680*A: Increased dose required. SLC22A1*3: is associated with decreased clearance of morphine CYP2D6*4/*4: decreased response, require higher dose
Fentanyl	CYP3A4, OPRM1	rs1799971*A/G	Poor CYP3A4*G-allele: increased plasma concentrations; require decreased dose r/t notably lower ED50
Dilaudid	Glucuronidation & CYP2C9	Rare	Ultra CYP2C9*: require a higher dose Poor CYP2C9*: increased plasma concentrations; require decreased dose
Remifentanil	5-HTT	rs25531	Lower 5-HTT expression = Greater analgesic effect

Anesthesia Medication Breakdown – Induction Drugs

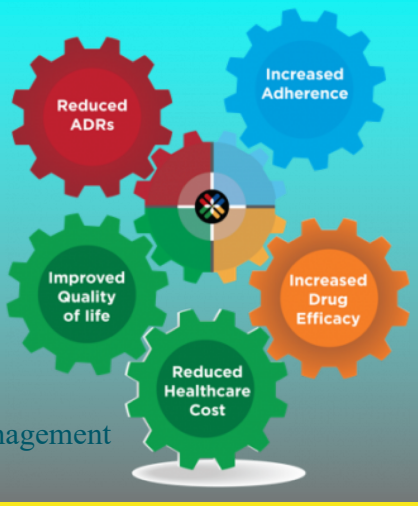
Medication	Gene Affected	Functional Variant	Effect of Polymorphisms
Midazolam	CYP3A4 CYP3A5	A>G	Decreased clearance
Propofol	CYP2C9 CYP2B6 UGTs	CYP2C9*1/*1 CYP2C9*2/*2 Genotype AA	-Poor: increased duration of action -Ultra: increased elimination -CYP2C9*1/*1 have decreased concentrations compared to CYP2C9*2/*2 -Genotype AA require decreased dose, have increased severity of hypotension
Ketamine	CYP2C9 CYP2D6	CYP2D6*6	-Poor: increased duration of action -Ultra: increased elimination -CYP2D6*6 decreased clearance
Ondansetron	CYP2D6 CYP3A4	CYP2D6*1xN CYP2D6*2xN	-Ultra: needs increased dose for desired effect -CYP2D6*1xN and CYP2D6*2xN have decreased response in women -Genotype CC has increased chances of vomiting
Precedex	CYP2A6	rs1800544*G	Allele G causes increased Ramsey sedation scores and longer periods of sleep compared to genotype CC

Anesthesia Medication Breakdown – Cardiac Medication

Medication	Gene Affected	Functional Variant	Effect of Polymorphisms
Labetalol	CYP2D6 ADRB1 ADRA2	Numerous CYP2D6, ADRB1*	Ultra: CYP2D6* require a higher dose
Metoprolol	CYP2D6 ADRB1	Numerous CYP2D6, ADRB1*	Ultra CYP2D6*: require a higher dose Poor CYP2D6*: increased plasma concentrations; require decreased dose
Phenylephrine	ADRB2	rs1042713*AA	Increased dose requirements for women with genotype AA

Implications for future practice

- Enhanced pain management
- Fewer ADRs
- Ameliorate patient outcomes
- Greater patient satisfaction
- Shorter hospital stays
- PGx becoming more mainstream
- Focus for hospital systems advertising tailored patient management



Conclusion

- Drug metabolism is not uniform
- Anesthesia providers need to adapt everyday to varying patient responses to medications
- Knowing ahead of time a patient's metabolic predispositions could decrease the incidence of ADRs and reduce the time taken for trial and error
- Improved patient outcomes and satisfaction
- Improved pain management
- Providing a more tailored anesthetic

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https://tinyurl.com/pgxposttest1

Appendix 12 – Post-educational Survey

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Deciphering Pharmacogenomic Implications for the Anesthesia Provider Post-intervention survey

Unique Numerical Identifier (Same number as for pre-test please): _____

Section 1: Experience and Attitude

1. Please rank.
   Pharmacogenomics is relevant to my current practice.
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

2. In general, on which of the following do you predominantly base your drug dosing? (select all that apply)
   - Body weight
   - Renal function
   - Liver function
   - Age
   - Pharmacogenomics
   - Comorbidities
   - Comedication
   - Other:

     _____

Section 2: Knowledge

3. Please rank your perceived knowledge on a scale.
   I am familiar with pharmacogenomics.
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

4. Where did you learn about this topic?
   - University
   - As a junior staff member
   - Conference
   - Journal
   - Internet
   - Never
   - Other:

     _____

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5. Please rank your perceived knowledge on a scale.
   I am familiar with the role of drug metabolizer phenotypes (e.g. a poor metabolizer).
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

6. Please rank your perceived knowledge on a scale.
   I am familiar with interpreting the results of pharmacogenomics tests.
   - 1 Disagree
   - 2
   - 3
   - 4 Agree

7. Where did you learn about this topic?
   - University
   - As a junior staff member
   - Conference
   - Journal
   - Internet
   - Never
   - Other: _____

Section 3: Knowledge Testing

Please answer the following questions to the best of your knowledge (select one answer only per question).

8. What may be the consequence of a pharmacogenomic polymorphism?
   - An individual cannot metabolize any drugs
   - An individual has a higher risk for toxicity when using prescription drugs
   - A single drug dose is appropriate for a given indication
   - Individualized dose adjustments should be made according to body surface area

9. What does a poor metabolizer (PM) phenotype indicate?
   - Lower drug safety because of poor metabolism
   - Good drug efficacy because of poor metabolism
   - Decreased enzyme activity
   - Increased enzyme activity

10. A person who is a PM for CYP-2D6 gets a medication that induces CYP-2D6. That may be a consequence?

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- Decreased CYP-2D6 activity
- No activity of CYP-2D6, no consequence
- Increased CYP-2D6 activity
- The person becomes an intermediate metabolizer (IM) for CYP-2D6

11. Please rank your perceived knowledge on a scale.
I am confident that I can use the results of pharmacogenomic tests to make an appropriate adjustment to a patient's drug therapy.
    - 1 Disagree
    - 2
    - 3
    - 4 Agree

12. To adjust therapy based on pharmacogenomic tests (more often) I would need… (select all that apply)
    - Better knowledge on pharmacology
    - Better knowledge of pharmacogenomics
    - Better knowledge of legal regulations
    - Insurance coverage
    - Other:

      _____

13. What would be your preferred format for learning more about pharmacogenomics in the future? (select all that apply)
    - Scientific article
    - Conference talk
    - Accredited learning course
    - Continuing medical education-accredited workshop
    - YouTube video
    - Medical app
    - E-learning course
    - Other:

      _____

14. How much time would you spend on an e-learning program on pharmacogenomics?
    - < 30 minutes
    - 30 minutes
    - 60 minutes
    - 90 minutes

15. What is your current age? _____

16. What is your title / profession?
    - SRNA
    - CRNA
    - MD/DO

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- Other: _____

17. What is your highest level of education completed?
    - BSN
    - Diploma
    - MSN
    - DNP
    - MD/DO
    - PhD

18. Number of years of anesthetic practice?
    - < 1
    - 1-2
    - 3-5
    - 6-10
    - 11-15
    - >15

19. Please list any additional comments or feedback here:

Thank you for your participation in our study,

Michael D. Daley and Julie S. Greenberg

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