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Clinical Utility of Pharmacogenomic Testing to Support Prescriptive Decision Making Among Anesthesia Providers: A Mixed-Method Study

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by

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Abstract

Anesthesia care is delivered world wide on a daily basis. Provision of anesthesia cares for surgical, obstetrical, or pain management procedures mandate a thorough understanding of physiology, pathophysiology, and pharmacology. Nearly 4 million anesthetics are delivered in the United States each year and the impact of genetics on anesthesia care is becoming greater. Anesthesia providers make prescriptive decisions based on an individual patient's disease processes, proposed surgical or therapeutic procedure, and a thorough clinical history. The age of personalized medicine is upon us and the ability to use genetic testing to help predict how a patient will respond to various medications is here. By using genetically coded single nucleotide polymorphism programming of the metabolic pathways in the liver, drugs responsiveness can be more precisely predicted and explained. This dissertation focuses on the clinical utility of genetic testing to predict drug responsiveness (pharmacogenomics) among anesthesia providers with a focus on treating acute pain. Specifically, the following research question is addressed: What is the clinical utility of pharmacogenomic testing to support prescriptive decision making among anesthesia providers. To answer this research question, a mixed-method sequential qualitative quantitative study was carried out. The conclusions of this research are (a) anesthesia providers lack knowledge concerning pharmacogenomic testing, (b) anesthesia providers are concerned about potential ethical and economic issues surrounding genetic testing, and (c) anesthesia providers perceive a potential benefit to using pharmacogenomic testing as it relates to making prescriptive decisions. Further work is necessary to more carefully refine the instrument used to measure clinical utility as well as future intervention work aimed at increasing anesthesia provider knowledge about pharmacogenomic testing.

Table of Contents

Chapter 1: Introduction

Knowledge in the Field of Study

Pharmacogenomic testing is becoming more widely used to help make personalized healthcare decisions, however, a stark gap exists in the literature about the perceived clinical utility of pharmacogenomic testing in supporting prescriptive decision-making in anesthesia practice. The majority of anesthetic pharmacogenomic testing lies focuses on the cytochrome P450 (CYP450) enzyme system that metabolize medications.[1] CYP450 enzymes are found primarily in the liver and their activity level is in some part responsible for how a patient will respond to a medication.[2-4] Although there is heterogeneity among patients current estimations purport 60 CYP450 pathways; replicated studies have shown six of these are responsible for 90% of all metabolism of all available medications.[1]

Each individual possesses a different CYP450 system that results in varied responses to medication between people.[1] Pharmacogenomic testing can help categorize how an individual's variation in genetic penetrance and expressivity will control for CYP450-mediated drug metabolism rates.[5] Traditionally, prescriptive decisions for medications are made mostly on a trial-and-error basis. These methods use sound science by combining what is individually known about a patient's physiology and pathophysiology so they are somewhat patient specific.[1] Unfortunately, this approach to making prescriptive decisions is not completely objective or accurate and the incidence of adverse drug events, unnecessary risk exposure, and elevating costs mandate the need to use better methods to inform clinical prescriptive decisions.

Current Practice

In the area of pain management, the administration of opioid analgesics to help control acute pain in the perioperative period is the mainstay of practice. It is well established that opioid analgesics carry significant risk even when administered at normally accepted doses.[6,7] The risks associated with opioid analgesics include respiratory depression, respiratory arrest, and even death. Additionally, the side effect profile of opioid analgesics is profound and can include pruritis, nausea, vomiting, constipation, urinary retention, and somnolence and can impact patient satisfaction and adherence to prescribed therapy.[5,8] Better and more patient-specific best practice methods are warranted as needed as they can help to avoid these possible severe events and diminish the more minor risks.

The ability to personalize care with pharmacogenomics is based on an individual's genetic profile (genotype) and the penetrance and expressivity of many different single nucleotide polymorphisms (SNP) that influence the way the liver metabolizes drugs through the CYP450 systems.[2] The specific concern for opioid analgesics is the CYP2D6/2C9 SNP that help control metabolism in a slow, fast, and ultra-fast manner.[2,3] Because the CYP2D6/2C9 SNP control for the metabolism of opioids, testing and interpretation of these genotypes can help the anesthesia provider better plan and dose opioids to achieve optimal analgesic effects without the burdensome and dangerous side effects typically seen with inappropriate opioid selection and dosing.[6] This will help to ensure the right drug is prescribed at the right dose in the right patient at the right time. By avoiding excessive doses of potentially lethal opioid analgesics in

patients with genotype-specific programmed slow opioid metabolism, adverse drug

events can be avoided.[6]
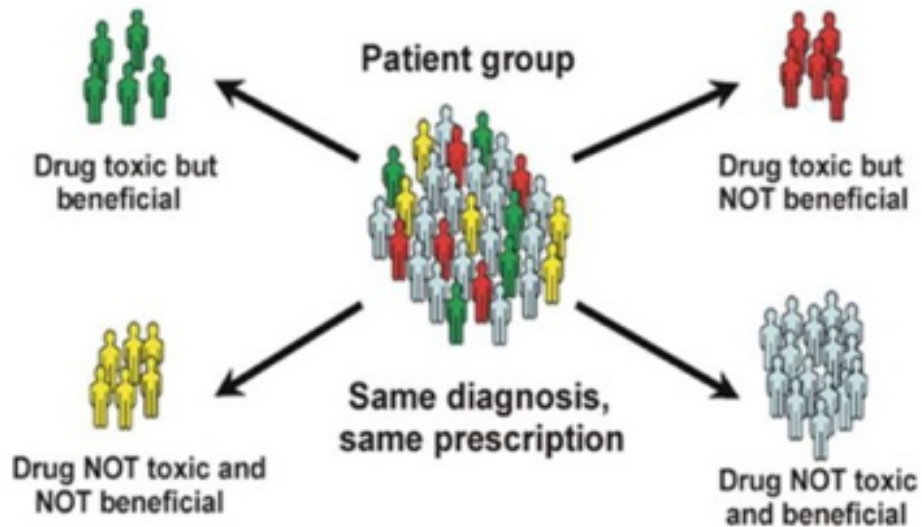
Figure 1. Four potential outcomes of medication administration

Pharmacogenomic Testing

There are many commercially available, low cost pharmacogenomic tests

available to practitioners to help inform prescriptive decision-making regarding

medications.[1] These tests include in-office testing for very specific SNPs or larger assays

that will help practitioners determine patient response to a large variety of medications.

Outcome studies demonstrate superior patient responses and decreased side effect

profiles when pharmacogenomic testing is used by practitioners to help understand

clinical prescriptive decisions; however, uptake by the healthcare community remains

extremely low.[2,6,7,9-14] The perceived clinical utility of pharmacogenomic testing,

specifically among anesthesia providers, is unknown. A gap exists in the literature

pervades regarding how anesthesia providers perceive clinical utility of

pharmacogenomic testing.

Clinical Utility

For a test, treatment, or technology to be considered useful it must be demonstrated that it has clinical utility.[15] To date, data exists of the perceived clinical utility of pharmacogenomic testing among healthcare providers as a whole and among family practice physicians, however, no studies exist demonstrating clinical utility of pharmacogenomic testing among anesthesia providers.[15,16 5,13,14,17-19] The feasibility of conducting clinical utility perception studies has been well-established, however, there are no data to demonstrate the knowledge, education, perceived benefits and barriers, and perception of pharmacogenomic testing use to inform prescriptive decision-making among anesthesia providers in the United States.

Pharmacogenomic Testing in Anesthesia

The purpose of manuscript one was to exploration of the concept of genetic predisposition as it related to healthcare decision-making.[20] An exhaustive literature review to explore the concept of genetic predisposition with the understanding that the concept of genetic predisposition is the underpinning science behind pharmacogenomic testing was conducted. It was discovered that the concept of genetic predisposition is immature overall but does have some degree of pragmatic maturity.[20] Based on this analysis, the concept of genetic predisposition can be defined as the use of genetic testing to predict disease, stratify risk, identify susceptibility and guide prevention of disease.[20]

The purpose of manuscript two was to complete an integrative review of the instruments currently used to measure acute pain. In order to measure a concept, in this case a physiologic concept of pain, an instrument with sound psychometrics is necessary. In order for an anesthesia provider to understand the effectiveness of an intervention

4

aimed at treating (or reducing) pain levels, appropriate instruments with sound psychometric measurements are necessary. In this review, it was determined that most clinically-used instruments to measure acute pain are not psychometrically solid, however, there are five instruments currently available that have moderate psychometric properties rendering them clinically useful for acute pain measurement.[21]

Despite an understanding of the concept of genetic predisposition and known psychometrically-sound instruments that can be used to measure acute pain, no data exists on the perceived clinical utility of pharmacogenomic testing among anesthesia providers. There are also no instruments that measure clinical utility of pharmacogenomic testing among anesthesia providers. The purpose of manuscript three of this dissertation, therefore, is to report on the results of a mixed-method study that aimed at describing the perceived clinical utility of pharmacogenomic testing among currently practicing anesthesia providers. Additionally, this manuscript reports on the fundamental psychometric testing of a yet-to-be developed future instrument aimed at measuring the degree of clinical utility of pharmacogenomic testing among anesthesia providers.

Theoretical Framework

The framework guiding this dissertation was the Centers for Disease Control and Prevention's (CDC) ACCE Model of Public Genomics.[22] In this model, the CDC has proposed a conceptual model for comprehensive evaluation of clinical utility of various types of genetic testing. The model's dimensions include analytic validity, clinical validity, clinical utility, and ethical, legal, and social implication of a genetic test. The specific portion of the model used in this dissertation is the outer ring of clinical utility.
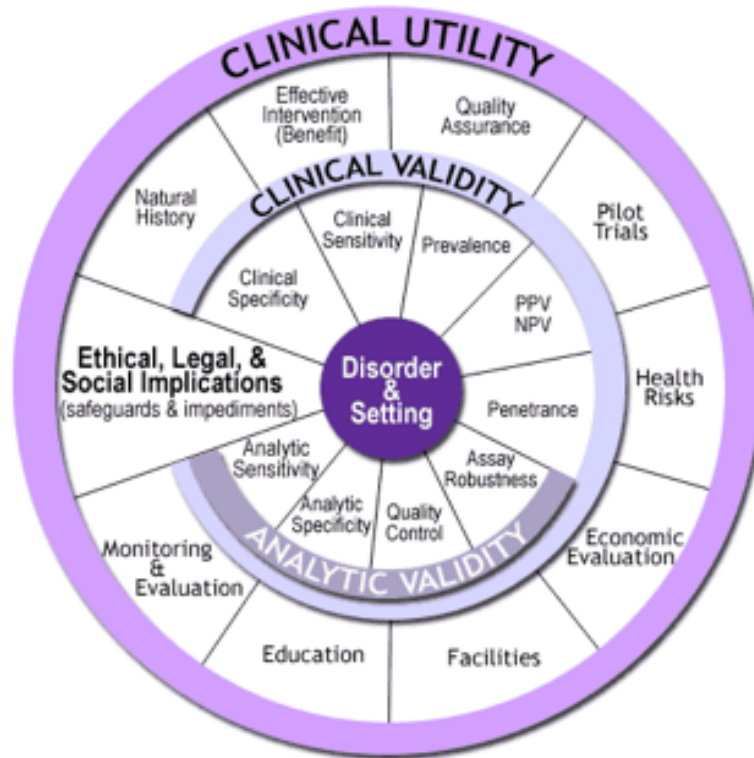
Figure 2. ACCE Model of Public Genomics

Collectively, the three manuscripts of this dissertation describe the clinical utility of a genetic test. The specific genetic test is pharmacogenomic testing as it relates to helping anesthesia providers make decisions about opioid analgesics to treat acute pain. Guided by the CDC ACCE Model of Public Genomics, this body of work seeks to answer the research question: What is the perceived clinical utility of pharmacogenomic testing among anesthesia providers?

Chapter 2: Genetic disposition: A principle-based concept analysis

Abstract

Aim. To report an analysis of the concept of genetic predisposition.

Background. The discipline of genetics has evolved tremendously in the past few decades. The impact of genetics on nursing practice and research is burgeoning and the concept of genetic predisposition is emerging in the literature.

Design. Concept analysis

Data sources. A total of seventeen articles in the English language are used.

Method. The principle-based concept analysis method was used to analyze the concept of genetic predisposition.

Results. Genetic predisposition has overall conceptual immaturity. The epistemological, linguistic, and logical principles all show mild to moderate maturity as related to genetic predisposition. The concept has pragmatic maturity with the caveat that the contextual placement of the concept be understood.

Conclusion. A definition of the concept of genetic predisposition is suggested as well as a direction for future research.

Keywords. Concept analysis, genetic predisposition, principle-based, nurse, nursing, genetics

Genetic Predisposition: A Principle-Based Concept Analysis

Within the profession of nursing, the incorporation of genetics into caring for patients has become almost commonplace in the past several years. The use of genetics includes diagnostics, screening, and helps inform clinical treatment decisions.[23] Within the emerging field of genetics, there lie several concepts that are frequently encountered such as genetic relevance, genomics, pharmacogenomics, and genetic testing. The goal of this paper is to add clarity to the concept of *genetic predisposition* through a formal concept analysis using the Principle Based Concept Analysis method. This method is chosen because it helps explain the current state of the science related to a concept and is useful when the concept is relatively immature.[24]

Concept Definition

Genetic predisposition is the combination of the terms 'genetics' and 'predisposition', each of which could be individually considered concepts but the combination of the two words leads to a third unique concept. Using many sources, this section aims to first define *genetics* and *predisposition* independently. After the independent definitions are examined, the concept of genetic predisposition as a whole will be explored.

Genetics, as defined by the *Oxford English Dictionary* (OED),[25] is the "scientific study of inherited variation in living organisms, and the cellular and molecular processes responsible for this." Furthermore, the OED specifies that the branch of biology concerned with studying inherited variation be called *genetics*. Historically, the term *genetics* first appeared in 1905 when scientists were trying to describe the study of heredity and the term genetics was agreed upon as the best definition.   The scientific

community agreed that the term *gene* would be used to describe the basic unit of heredity with *genetics* being the study of heredity. In 1968, the *New England Journal of Medicine* first published a scientific paper about the genetics of alpha1-antritypsin deficiency and used the term *genetics* to describe the cause of this protein deficiency.[25]

 Predisposition is a term defined as the pre-existing tendency to suffer from a disease of medical condition.[26] Its use dates back to 1622 when Henry VII was described as having the "sweating sickness" as a result of the *predisposition* of the seasons. Later in 1707, physicians began using the term *predisposition* to describe a patient's likelihood of contracting a disease based on their family history of a similar disease. In this century, the term *predisposition* has been used to describe someone who is pre-symptomatic for a disease but has not yet demonstrated clinical signs for the particular disease.[26] An example of this is a person who has a family history of diabetes but has yet to have elevated blood glucose levels.[27]

 In order to define genetic predisposition, the combination of *genetics* and *predisposition* must be used. For the purposes of this submission, combining these words gives *genetic predisposition* the following meaning: a preexisting tendency to suffer a disease or medical condition based upon inherited variations of living organisms. Stated another way, *genetic predisposition* is the likelihood of having a disease or medical condition as determined by specific cellular or molecular markers that have been inherited.

Other Definitions

 The concept of *genetic predisposition* is widely used in scientific literature regarding the study of genetics. In the arena of primary genetic research, scientists use

the term *genetic predisposition* to describe the molecular and cellular markers of disease.[28] In this context, *genetic predisposition* has no human element but rather the results of a genetic testing profile that is paired with a disease process. Thus, there is no particular relationship between a test result and a patient; it is simply an example of statistics indicating result X will mean disease Y has a high probability of occurring.[28] In this realm, genetic predisposition could be considered a cold, isolated concept.

Elsewhere, when the term *genetic predisposition* is used, scientists are referring to a particular patient or set of patients. There are known genetic tests that will yield results related to specific diseases. The concept of genetic predisposition, in this case, is used to describe those patients at risk for developing the disease in question.[29] In this light, *genetic predisposition* is a proposition of what might happen or what could happen based on genetic profiling.[30] One example of a disease is epilepsy and the various genetic tests for the disease. Emerging as a central focus of epilepsy research, genetic testing has identified more than 20 genes thought responsible for epilepsy.[29] Patients possessing one or more of these particular genes are considered to have a *genetic predisposition* for development of epilepsy.

Another use of the concept of *genetic predisposition* is not found in the biological science literature but rather in social science and theological literature. In this venue, *genetic predisposition* is seen through the lens of vulnerability and the unknown.[31] In this light, the concept of *genetic predisposition* is highly correlated with risk; that is to say *genetic predisposition* is inherently paired with a risk for disease and comorbidity.[31] Using genetic testing to determine the risk of developing cancer highlights an example of this use of *genetic predisposition*. There are many in the population that would not like

to know this information and by receiving such testing for genetic markers of cancer significant psychological harm may occur.[31]

A final use of *genetic predisposition* is centered on the idea of susceptibility or vulnerability. In this context, *genetic predisposition* refers to the anticipated response to a drug or treatment.[28] An example of this would be the use of genetic testing to determine a patients *genetic predisposition* to the effects of opioid pain medication.[9] In this context, *genetic predisposition* can help predict adverse or unwanted side effects of medications. Testing can be performed to help inform clinical decision making to ensure the best possible patient outcome.

Conceptual Framework

Genetic predisposition can be grounded in the Systems Biology Conceptual Framework. Systems biology poses that science is derived from interdisciplinary study of complex systems and then synthesized to investigate cellular-level biological processes.[32] This approach is holistic and involves specific applications to the study of genes, their proteins for which they code, and the resulting phenotype. Specific to genetics research, the Systems Biology Framework allows for a strategy to study diseases with a genetic basis. Interdisciplinary teams of nurses, physicians, epidemiologists, and biostatisticians can work together using one conceptual framework.[32]

In the Systems Biology Framework, the nurse scientist assumes that one intervention can result in a dynamic process in multiple levels of the person such as the genetic, molecular, cellular, and organ system level.[32] In application to genetics, it is Systems Biology Theory that says genetics could have an impact on disease initiation or progression. An important aspect of Systems Biology Theory allows for the impact of

environment and intervention to impact the resulting disease.[32] Studies undertaken using

Systems Biology Theory help to understand the complex interaction of genes and their

impact on disease progression and treatment. A conceptual model of Systems Biology

Theory is listed below, Figure 1.

Figure 1. Systems Biology Conceptual Model
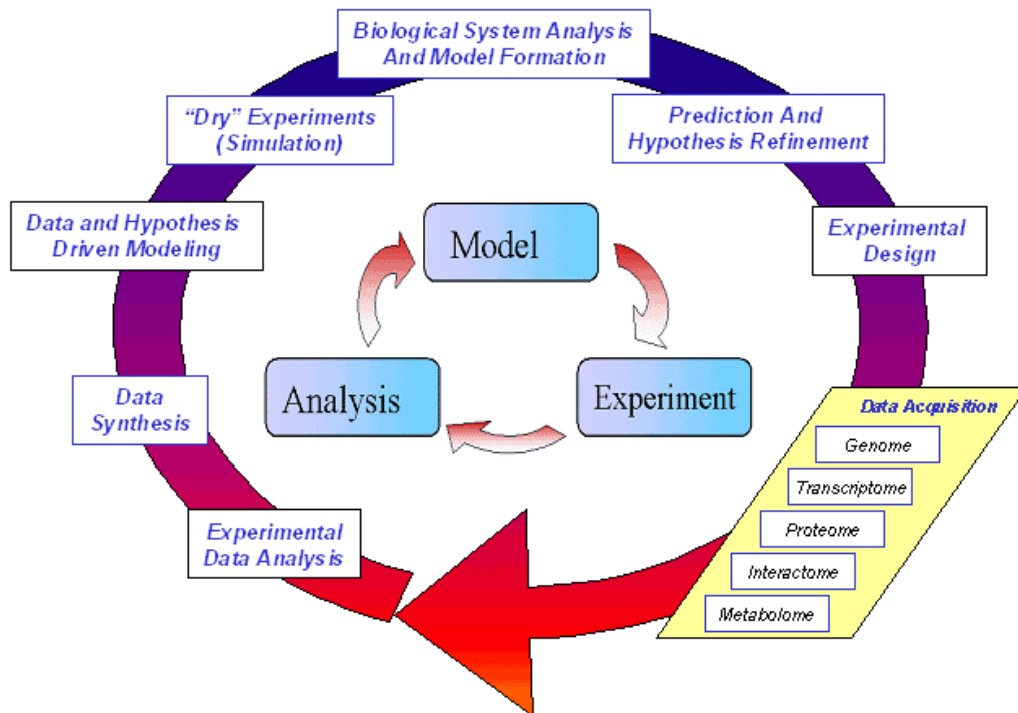
Literature Review

Structure of Search

A purposeful and exhaustive literature search is obligatory to increase rigor and

decrease bias in a concept analysis.[33] A three-step search strategy was utilized in this

concept analysis. An initial limited search of MEDLINE and CINAHL was undertaken

followed by analysis of the text words contained in the title and abstract, and of the index

terms used to describe the article. This search was performed to identify historical views

of *genetic predisposition.* A second search using all identified keywords and index terms

were undertaken across all included databases. Thirdly, the reference list of all identified reports and articles was searched for additional studies.

Databases included in the exhaustive search included EBSCOhost (CINAHL, MedLine, eBook Collection, and MasterFILE Premier), PubMed, Science Direct, and Pro Quest. Libraries from two universities were utilized as well as the assistance of a reference librarian to help define search terms and Boolean phrases appropriate to the concept. The search was limited to articles in English language only as translation services are not available. Additionally, only articles discussing human subjects were included. There are numerous studies that speak to *genetic predisposition* in animal and plant species as well. The timeframe for the search was 1950 through October 2012. All articles were retrieved either electronically or through interlibrary loan services.

Search Results

The initial search was in the EBSCOhost database that includes CINAHL, MedLine, eBook Collection and MasterFILE Premier search engines. Keywords used included genetic predisposition, genetic AND predisposition, gene* predisposition, and "genetic predisposition" in all data fields. The searches were limited to English language and human subjects only. This search strategy resulted in a total of 722 articles.

The next search was in the ProQuest database. Keywords used were genetic predisposition, "genetic predisposition", and genetic AND predisposition. Again, the language was limited to English and human subjects were only examined. This search strategy results in 233 articles for consideration.

The final literature search was using Science Direct. The keywords included genetic predisposition, "genetic predisposition", and gene* predisposition. Limiting this

search to English language only, a total of 110 articles were returned. After looking closely at these articles, 20 were excluded in this initial search based on non-human subjects. Therefore, Science Direct yielded 90 articles for the purposes of this concept analysis.

A total of 1822 articles were retrieved using the outlined search strategy. An initial review of the title allowed for exclusion of 1451 articles. The abstracts of the remaining 371 articles were then read and considered. Studies includes in this analysis must have distinctly discussed genetic predisposition and defined some aspect of the meaning of this term. Many studies retrieved that mentioned genetic predisposition but after careful analysis these studies did not speak comprehensively about this term. Additional articles were excluded from analysis because they were editorial statements. Included in the literature matrix are primary research studies and review articles speaking directly to the concept of genetic predisposition. This process resulted in 17 articles for analysis. The details for each article are presented in Table 1, below.

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
Predictive	[15]	-genetics can forecast what might happen -predisposition is seen as development of disease/condition	-None, integrative review article with meta-analysis calculations	-Can genetic biomarkers determine drug-induced liver injury? -review article	-genetics can help predict liver injury (often highly predictable) but not guarantee results	-review article looking at 12 primary research articles -no detailed search strategy noted
	[34]	-well defined genetic events/mutations can show progression to cancer -predictability of genetic mutations in a particular sequence	-None, integrative review article	-What are the defined mechanisms involved in genetic predisposition to development of colorectal cancer? -review article	-step-wise progression of gene polymorphisms predicts colorectal cancer -gene-environment and gene-gene interaction is highly correlated with cancer development	-exhaustive literature search -well defined inclusion/exclusion criteria -differentiated between high and low penetrance genetic mutations
	[31]	-prediction of disease (focus on cancer) -prevention of disease based on results of testing -genetic testing can be seen like mammogram and pap smear – testing for disease that's preventable if treated	-to test a model of intentions based on theory of reasoned action -n=1824 adults, recruited from across U.S. -outcome was behavioral intention (intent to get genetic testing)	-What is the influence of religion on decisions to undergo genetic testing? -4 hypotheses tested	-religion affiliation results in negative feelings towards genetic testing -if question was phrased as "disease is completely treatable and GT can predispose you to good treatment" then high correlation with testing	-interesting study looking at religion, previous experiences, and question wording on attitudes about genetic testing -not all hypotheses were completely clear or addressed in discussion/conclusion

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	[35]	-likelihood of development of side-effects from medication -predictability of drug performance -seen as a positive predictive factor	-pilot study, n=109 -all morbidly obese patients -looked at 3 SNPs associated with morphine metabolism -wanted to define a candidate gene responsible for morphine pharmacodynamics	-Is there a gene implied in opioid pharmacodynamics in obese patients?	-3 SNPs were found among the group -A118G was seen in higher frequency in obese population compared to general population -presence of this SNP may be predictive of opioid effectiveness and possibility of side-effects	-pilot study so results are not generalizable to entire population or even all obese patients -very clear that further testing on this gene in obese patients needs to be conducted to determine clinical relevancy
	[36]	-forecasting of disease -filtering of genetic information to determine highest prediction rate of disease -identification of those with disease earlier	-feasibility study, n=50 -recruited patients from the Familial Breast Cancer Study -prospective, cohort study	-Explore feasibility of using gene exome sequencing technique to predict breast cancer rates	-exome sequencing is revolutionary in identifying rare genetic variants -predisposition to disease may be better determined by exome sequencing -feasible to use this technique, exact methods need further investigation	-utility of this technique is not fully known -spoke extensively of prediction power of genetic testing as the predisposition to disease -results not generalizable nor clinically useful yet until further techniques are developed

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	[37]	-prediction of suicide is related to genetic markers -ability to help determine who is going to have suicidal behavior	-none, literature review	-Is there a genetic predisposition to suicide?	-high correlation between genetics and mood disorders and suicide -not enough evidence to suggest an association between genetics and suicide	-excellent inclusion of varying studies -controlling for extraneous variables in inclusion criteria gave strength to conclusions
Risk	[38]	-incidence of disease development -factors, including genetics, contribute to diagnosis	-n=17.035 -nested-case control prospective cohort study	-Is there an association between SNPs and breast cancer – based on age and parity?	-6 distinct SNPs do put patients at higher risk of development of breast cancer -no association with age or parity	-huge sample size -all women in Sweden born between 1923-1950 invited to participate -results only applicable to women of northern European origin?
	[39]	-incidence of disease -determining the patient at most risk -assessment of probability	-integrative review article	-What is the current state of the science regarding genetic predisposition to malignant melanoma	-risk stratification based on a particular set of high risk, medium risk, and low risk genetic markers	-excellent review of molecular risk assessment strategies -poorly described literature review process

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	[29]	-risk associated with need for further testing -incorporation with heredity and environment determines absolute risk -relative risk, awareness	-review article	-What is the current state of the science regarding genetic testing (BRAC1/BRAC2) and breast/ovarian cancer	-BRCA1/BRCA2 determine molecular basis of disease -should not be used for overall population screening -results are a basis for determining risk estimation	-great review of the physiology of cancer -excellent literature review -defined predisposition and risk well
	[30]	-disease development is inherently bad/negative -genetic testing can show risk of potential negative outcomes -genes do not completely show risk, interaction with environment and lifestyle are needed	-None, integrative review article	-What is the current state of the science regarding genes and cardiac disease?	-23 of 33 previously thought of genetic loci do not increase risk of CAD -CAD is propagated by factors other than pure genetics -lifestyle and environment play big role in development of CAD -predictive genetic variants are not ready for routine testing	-interesting insight into the need to back down from genetic testing until the science is more solid -good explanation about what was know and why that is now being dismissed -discussed risk as very negative and decreasing risk as very positive

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	[16]	-genetic testing help stratify risk of disease -knowing results can decrease anxiety, though risk is still present -genetics and environment complete the risk profile	-Qualitative study design -n=40 in depth interviews -from previous sample of epilepsy study group at Columbia University	-How do people with epilepsy and their family members understand genetics? -How do people with epilepsy and their family members perceive risks and benefits of genetic testing? -What do people's hope and fears regarding genetic testing reveal about the local moral worlds of people with epilepsy?	-revealed people want more information about ontology of epilepsy -universally genetics is seen as risk stratification -most felt genetic testing offered benefits in knowledge and lifestyle issues including reproduction	-insightful study examining people's understanding of genetics as a whole -theme of reproduction (heritability) emerged which was seen as an unexpected finding
	[31]	-genetic makeup can predict risk of disease -genetic makeup can be protective in some cases -genetics can help explain clinical progression	-pilot study -prospective, cohort study -n=93 patients -all had ESRD -regression analysis, ANOVA, and Pearson correlations used	-Pilot study to determine an association between genetics, ESRD, and depression development	-association between certain SNPs (AA variant) and development of depression -seen as a risk (if AA, then risk of developing depression is higher)	-excellent study design, comprehensive statistical analysis -pilot study, limited results

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	[32]	-dyslipidemia is associated with DM-2 -genetic makeup can show risk for developing dyslipidemia and ultimately DM-2 -risk is based on the genetic makeup	-nested, cohort study -n=5,499 -examined specific lipid loci in study and control patients -examined more than specific SNPs, tested for gene-wide loci for lipid production	-Investigate the association between genetic predisposition to dyslipidemia and DM-2 development	-significant increase in risk of developing DM-2 with certain genetic markers of dyslipidemia -difficult to estimate exactly based on poor mapping of some genes coding for lipids	-large sample size -well constructed treatment and control groups -question the comparison of US and European populations as treatment/control comparisons
Susceptibility	[33]	-certain genes render a patient susceptible to a disease -patterns of expression lead to higher rates of disease	-metaanalysis of 12 primary studies -calculated OR and CI for all studies -overall found a high and low frequency gene related to lung cancer	-Metaanalysis of 12 primary studies -Is there a single gene that show patient susceptibility to lung cancer?	-no single gene is responsible for lung cancer -two high-penetrant, low-frequency genes are association with development of lung cancer	-well done statistical analysis -calculated CI for each study to add strength to final statement -strict inclusion/exclusion criteria

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	34	-genes contribute considerably to disease -protection from and susceptibility to disease are seen -genes influence MS susceptibility	-n=1784 -cohort study, case-controlled -correlational statistics looking at MS and genetic makeup -convenience sample of patients at 3 clinics with known MS	-Aim was to investigate association to multiple sclerosis all three classes of HLA I genes	-2 of the 3 HLA classes predispose patient to MS -1 HLA gene presence offers protection from development of MS	-poor/minimal discussion section -excellent description of the problem statement -excellent statistical analysis
	35	-susceptibility is the strongest term that can be applied to genetic testing -associations between genetic markers and disease -environment plays a huge part in disease	-none, narrative review article	-To discuss the association between genes and diabetes	-multiple genetic markers are associated with IDDM -not enough data to determine distinct predisposition marker -overlap between IDDM and other diseases in genetic markers	-good overview of the science of genetic predisposition -individual genetic variation conferred incomplete risk or susceptibility to disease

Attribute	Articles	Description of Concept	Measurement/Study Design	Study Purpose/Question	Results	Critique
	[36]	-genetic predisposition to obesity has been established -physical activity attenuates this susceptibility based on genetics -environment, activity, and lifestyle play a large role in development of disease	-prospective, population study -n=20,000 -genotyped for 12 SNPs known to increase BMI	-Can the genetic predisposition to obesity be modified by physical activity	-those people with genetic markers for obesity can reduce incidence of obesity by 40% with physical activity -lifestyle modification can be powerful in altering genetic predisposition	-large, population based study -limited to the European population, not across all populations

Analysis of Concept

The question to be addressed in this analysis is: "What is the current state of the science regarding the concept of genetic predisposition"? A principle-based concept analysis method is employed to perform this analysis. The basis of the principle-based concept analysis is evaluation of the concept in four key areas: epistemological, pragmatic, linguistic, and logical.[24] It is through these four principles that the concept can be evaluated and the state of the science surrounding genetic predisposition as a concept can be established. For the purposes of this analysis, the four undergirding principles will be addressed individually and attention will be given to defining the concept of genetic predisposition as a statement of the state of the science.

Epistemological

The epistemological principle refers to the nature of knowledge.[24] When examining the epistemological principle, a determination of the concept's clarity and differentiation from other concepts is analyzed. Genetic predisposition is not clearly defined nor well differentiated from other concepts. Lack of clear definition is partly due to the relatively immature nature of genetic predisposition.[12] Literature can be grouped into three overarching themes associated with the definition of genetic predisposition: predictive, risk and susceptibility to disease. These three terms have different meanings that are often based on the context in which they are discussed.

In order for a concept to be considered mature, it must be clearly positioned in the body of literature.[24] The concept of genetic predisposition is not well situated in the literature and is not well-differentiated form other descriptions of risk or prediction. Lack of the clear definition of genetic predisposition is based partly on a lack of understanding

of the exact mechanisms of disease development and progression.[16] Additionally, genetic

predisposition can be viewed in a negative connotation as in the risk of disease

development while other authors discuss genetic predisposition as being predictive of

health. [38,40,41] Because of the lack of clear definition, it is difficult to distinguish the

concept from others in the literature and is considered epistemologically immature.

Pragmatic

The pragmatic principle asks if the concept is useful and applicable in the

scientific community.[24] To address this principle, the concept was analyzed from a

historical perspective looking longitudinally at the literature. As the concept of genetic

predisposition has evolved, the usefulness becomes increasingly apparent. Earlier work

on genetic predisposition was reluctant to make definitive claims about the usefulness of

genetics in predicting outcome.[37] As the science of genetics has evolved and a greater

understanding of the human genome is realized, the usefulness of the concept of genetic

predisposition has been realized to help stratify risk, predict disease development, and

determine susceptible patients.[15,29,42,43]

Several studies have examined the utility of genetic predisposition to help predict

and stratify risk associated with disease development.[15,31,34,39,44] Specific diseases include

colorectal cancer, breast cancer, and diabetes; all of which have been shown to have a

genetic component. This is useful to the practitioner to help stratify risk and plan

treatment along with suggestions for lifestyle modification to decrease risk.[36] Also

emerging in the literature is the idea of genetic predisposition as a screening tool to be

useful at behavior modification. In this sense, genetic predisposition can be useful to

help predict outcome from treatments or to determine lifestyle modifications to reduce disease severity or development.

Linguistic

The linguistic principle asks if the concept is used consistently throughout the literature with attention to the meaning of the concept.[24] In this regard, genetic predisposition has poor linguistic maturity. It is seen used to describe risk, predict outcome, and determine susceptibility. The context in which the concept is used will determine the meaning of genetic predisposition. For example, if examining the risk of developing a disease, genetic predisposition has a negative connotation, as it is though to be predictive of disease formation.[36] Conversely, genetic predisposition can be seen to represent hope when used to show how disease development can be halted or reversed with lifestyle and environmental alterations.[43,45,46]

The concept of genetic predisposition has been applied in several contexts across varying patient populations and environments. Although many studies focus on the use of genetic predisposition in describing risk, there are other studies and review articles that look at genetic predisposition to help stratify risk and determine susceptibility to disease. Many terms and meanings can be seen used for the concept of genetic predisposition and varying interpretations of these meanings makes the concept of genetic predisposition linguistically immature.

Logical

The logical principle aims to determine if the concept of genetic predisposition remains clear and holds its boundaries when integrated with other concepts.[24] Because the epistemological principle lacks clarity, there is an impact on the logical principle.[24]

The analysis of the concept of genetic predisposition revealed that it is not well differentiated in the literature so it cannot have clear boundaries compared with other concepts. There are obvious overlaps between risk, prediction, and susceptibility all of which make up genetic predisposition as a concept. This overlap creates ambiguity for the concept and blurred boundaries when compared to similar concepts in the literature.

Limitations

Limitations to this concept analysis should be considered. The exclusion of articles not in the English language limited the body of literature reviewed. Additionally, the majority of articles selected were from medicine and genetics literature; there was a paucity of literature in nursing, pharmacology, and the social sciences. Studies were selected based on the inclusion criteria set forth above and no formal critique of the quality of the studies was performed. Several of the included studies were review articles, some with good methodological quality for searching and performing meta-analysis. Other review articles were integrative or narrative reviews and their findings lack the weight of higher quality reviews. There were no identified systematic reviews for inclusion.

Conclusion

The principle-based concept analysis of the concept of genetic predisposition has revealed an immature, although developing concept. Genetic predisposition lacks epistemological, linguistic, and logical maturity but does have pragmatic maturity and usefulness. Based on this analysis, the concept of genetic predisposition can be defined as the use of genetic testing to predict disease, stratify risk, identify susceptibility and guide prevention of disease. Further research into the usefulness of genetic

predisposition from the patient perspective would prove invaluable in advancing the

concept. Understanding the patient's perception of genetic predisposition and applying

this understanding to planning care and screening tools would be beneficial.

Chapter 3: Instruments to measure acute pain: An integrative review

Abstract

Context: Acute pain impacts approximately 45% of the world's population and is a cause of delayed discharge and increased cost to the healthcare system. If not appropriately treated, acute pain can transition into chronic pain resulting in long-term complications.

Objectives: The objective of this integrative review is to synthesize and describe the current instruments used to measure acute pain.

Methods: A systematic three-stage search strategy was used to review the literature.

Results: A total of 1754 manuscripts were identified with 8 meeting all inclusion criteria. Many of the instruments report various aspects of psychometrics but only 5 report reliability, validity, and address feasibility.

Conclusions: Caution should be exercised when using the currently available instruments to measure acute pain. Since treatment decisions are often based solely on the pain measurement instrument, it is important to ensure the chosen instrument is both reliable and valid.

Key Words: acute pain, instrument, review, psychometrics, integrative review

Introduction

Pain, as a concept, is an unpleasant or unwanted feeling often brought on by an injury or illness.[47] It is estimated that approximately 50% of the American population suffers from some form of acute or chronic pain.[6] Within the past few years, there has been a push internationally to think of pain as the "Fifth Vital Sign" signifying its importance to both the patient and healthcare provider.[48] Physiological implications of pain include: increased catecholamine release, changes in intrinsic cortisol levels, and delayed wound healing as well as psychological problems like depression and anxiety [49,50].

Pain is typically considered subjective, can be defined by the person experiencing it and can be described in multiple different ways. Theoretically, pain is defined as an aversive, uncomfortable, and unwanted sensation.[51] To operationally define pain a score or rating on a particular measurement scale is often used. Given the heterogeneity of individual pain perceptions, the measurement of pain as a construct has been labeled difficult to accurately measure.[52]

There are several defined types of pain including acute, chronic, and neuropathic pain. The focus of this review is to critically review the clinically used instruments that are aimed or focus on measuring acute pain. Acute pain is often defined as the normal physiologic response to adverse physical stimulus such as trauma, surgery, and acute illness.[53] The patient's self-reported pain score often predicates treatment of acute pain and there are several instruments in use clinically that purport to measure pain. The purpose of this integrative literature review is to synthesize the best available evidence related to quantitative instruments used to measure acute pain.

Theoretical Framework

      Currently, several theories informing the study and pathophysiology of pain. As proposed originally by Melzack and Wall, the gate control theory of pain proposes that there is a natural physiologic factor (gate) that modulates pain impulses within the spinal cord.[54] When a noxious impulse is perceived, large nerve fibers inhibit the transmission of some of the stimulus to the brain through afferent nerve tracts. The gate, or large nerve fibers, are effectively closed at this point and stimulation of the dorsal horn neurons of the spinal cord does not occur and the perception of pain is decreased.[55]

      The gating mechanism is influenced by nerve transmission descending from the brain and this mechanism is though to explain some aspects of normal physiologic functioning in the face of pain.[54] Factors influencing the gating mechanism include the amount of activity of pain fibers, the presence of analgesic medications, and emotional factors such as depression and mood.[56] Although the gate control theory of pain does not explain everything regarding pain, an in-depth study of this framework does explain why various medications and treatment modalities are effective in controlling pain. Within the current literature, the gate control theory of pain is one of the accepted frameworks.

Search Strategy

      Using a three-step search strategy, the literature was queried to find relevant and related studies. Consultation with a health science reference librarian was utilized to hone and refine the search terms and databases. In the first step of the search, the key words "measurement" and "pain" were used in the Cumulative Index to Nursing and Allied Health (CINAHL) and MEDLINE databases to ascertain relevant articles and additional key words related to the concept of interest. In the next step of the search

strategy, all identified key words including *acute pain*, *measurement*, *instrument*, and *self-report* were utilized across CINAHL, MEDLINE, PUBMED, and PsychINFO databases. In the third step of the search, the reference list of all articles meeting inclusion criteria was searched for additional manuscripts. Figure 1 represents the search strategy and articles found with each step. Of note, one article was not found using a database search; instead the article was shared by a colleague and is included as it meets inclusion criteria.[57] Overall, eight articles were utilized in this integrative review and Table 1 represents the relevant findings from those articles.

For the purposes of this literature review, the focus was on instruments that are self-reported measures of acute pain levels. Instruments that are designed for use in sedated or cognitively impaired individuals were excluded. Additionally, as the focus of this review was the adult population, studies related to instruments for use specifically in children were also excluded. Lastly, only instruments that were available in the English language were examined. There are several studies that address the psychometric evaluation of instruments for application in other languages; these studies were excluded, as no translational services are available. There was no date-limit set for this literature search.

Results

Each of the 8 studies included in this literature review represents a self-reported method of measurement of acute pain. Seven of the eight studies were conducted in the United States and one was conducted in England. Overall, the quality of the studies was fair with medium to low-level evidence informing these results.[58] The combination of these eight studies represents 1,278 total study participants. Only two of the eight studies

reported a theoretical framework for their study design.[59,60] Three of the eight studies

reported information on a newly developed scale aimed at measuring acute pain.[57,59,61]

The remaining five studies examined psychometric properties of existing instruments

with new applications or revised designs. Specific psychometric properties of the eight

included studies are reported in Table 1.

Reliability

Seven of the eight studies report some measure of reliability. In pain management

research, reliability is commonly measured in reliability coefficients, which is a measure

of stability and consistency over time.[62] This is commonly reported as Cronbach's alpha.

Six of the eight studies report reliability in terms of internal consistency with Cronbach's

alpha scores. Consistently, the measures of internal consistency as represented by

Cronbach's alpha are high (>0.95) across all six studies. The Visual Analog for Pain

study used Interclass Correlation Coefficient (ICC) scores between one-minute

measurements and the McGill Pain Questionnaire study performed three confirmatory

factor analysis models to test for reliability. [63,64]

Validity

Seven of the eight studies report validity results with varying methods for

calculating and reporting validity. Two studies reported strong validity but did not

provide psychometric calculations to support this statement. The remaining five studies

reported validity primarily using factors analysis and are reporting convergent validity.

Where reported, various validity scores are strong but often-exact statistical measures are

not specifically reported in the manuscript.

Discussion

     This integrative review found eight unique scales that measure acute pain. Previous reviews on pain instruments have been broad in scope and have not examined pain instruments related specifically to acute pain; therefore, the included eight studies represent only those instruments for which studies have examined psychometric properties for measurement of acute pain. According to this literature review, the McGill Pain Questionnaire and the Visual Analog Scale for Pain are the two most commonly used pain instruments in the clinical setting.[65]

     Strong reliability scores have been reported in most of the included studies; psychometric scoring for validity is sparse. There are many studies that indicated the instrument is valid but did not provide supporting evidence to the reader. As pain is a subjective concept necessitating patient reported scores for quantification, the lack of consistent validity scores raises concerns. As validity of a scale is foundationally a measure of how well the instrument measures what it purports to measure, it is possible that those instruments with no validity scores are not actually measuring pain but some other construct.

     Although reliability was shown to be strong across the entire included instruments, the lack of consistent reporting of validity raises concern. This is especially important when considering clinical implications of pain management. As a subjective concept, pain can only be measured indirectly by asking the patient about his or her pain levels. To measure pain, it is necessary to use an instrument to quantify the pain level, which is individualized. Treatment decisions and patient care are planned based on the reported pain levels. If an instrument is used that does not have adequate validity, there

is a danger of reporting a score that is not a true representation of the construct being measured. In this situation, potent and lethal medications could be administered and inappropriate discharge planning, or incorrect pain management procedures could be performed based on an erroneous pain score.

Additionally, many studies have shown that pain is far more complex than what is represented by a single score.[12,50] In measuring pain, this balance between a simple, quick, and useful instrument and an instrument that is comprehensive enough to measure the multiple facets of pain is difficult. This balance can be seen in this review by examining 1-item instruments, like the PAULA scale, as compared to an instrument like the MAPS scale that includes 101-items and requires considerable time to complete.[60,66] The key to finding an appropriate and useful instrument to measure pain is finding an instrument that is comprehensive enough to capture all of the facets of pain, short enough not to be burdensome to the patient, and has applicability to a wide range of the population.

One additional consideration that is not addressed in any of the studies is the phenomenon of sedation related to pain treatment. Frequently, acute pain is treated with medication that can cause sedation; sometimes this sedation can be profound. None of the studies examined the feasibility of using the instrument with a patient who is being actively treated for acute pain episodes. This raises concerns regarding the reliability of the instrument across the spectrum of an episode of acute pain. A clinical example is the patient in the immediate post-operative period receiving opioid analgesics for acute surgical pain. Although important to measure pain in this particular population,

reliability of the various available instruments has not been established in the face of a sedated patient.

Further research aimed at establishing validity of the various instrument used to measure acute pain is warranted. When clinical treatment decisions are based largely on scores obtained from pain instruments, it is of paramount importance to ensure the instruments are indeed measuring the construct of pain and not some other construct. This is critically important given the untoward side effects of the most commonly used treatment for acute pain: opioid analgesics.[3] The side effect profile of opioid analgesics can range from bothersome pruritus and constipation to severe respiratory depression and respiratory arrest.[67] Given the significant and dangerous side effects of the treatment of acute pain, it is essential that the instruments used to measure the construct on which treatment is based be reliable and valid for that construct.

Conclusion

There are several instruments available to measure the construct of pain. Of the eight reviewed instruments, only five have reliability and validity that would warrant clinical applicability. It is useful to have a varying and wide array of instruments that will fit with various populations. It is incumbent on the person administering the instrument, however, to make sure that it is reliable, valid, and applicable to the population in question. Fortunately, several instruments with excellent validity and reliability are feasible to use in measuring pain.

Disclosures and Acknowledgement

Table 1. Data extraction and psychometric properties

| Instrument Reference	Framework	Sample Subjects	Instrument Description and Scoring	Reliability	Validity	Feasibility	Level of Evidence[58]
Brief Pain Inventory Revised (BPI-R): [68]	Not reported	Adult surgical cancer patients at two VA hospitals in the US, n = 388	23-item self-report with response categories of 0-10 ordinal scale; higher number indicating more intense pain; 15 minutes to complete	Cronbach's alpha = 0.95 for medical patients Cronbach's alpha = 0.97 for surgical patients	Calculated by comparing BPI with VAS; Pearson correlation coefficients = 0.70 for medical patients; 0.60 for surgical patients	Reasonable, only 15 minutes to complete the 23-items; free instrument to use	2b
Brief Pain Inventory (BPI): [62]	Not reported	Adults with bone metastases receiving palliative radiotherapy for acute bone pain, n = 45	11-item questionnaire with response categories 0-10 ordinal scale with 0 = no pain and 10 = worst pain possible including one question asking for list of medications	Cronbach's alpha = 0.950 for worst pain scores; 0.939 for average pain scores; and 0.939 for current pain scores	Reported as having strong validity with high correlation coefficients	Short, 11 item questionnaire applicable to metastatic cancer patient with acute bone pain	2b

Instrument Reference	Framework	Sample Subjects	Instrument Description and Scoring	Reliability	Validity	Feasibility	Level of Evidence[58]
PAULA the PAIN-METER (PAULA): [66]	Not reported	Adult patients in the post-anesthesia care unit having undergone surgery, n = 65	Sliding ruler designed to be moved by the patient corresponding to level of perceived pain with response categories of 5 colored faces representing pain intensity	Internal consistency Cronbach's alpha = 0.98	Not reported	Simple, slide rule design but only measures one aspect of pain. One-item instrument might be at risk for poor content validity.	2b
Continuous Pain Score Meter (CPSM): [59]	Bio-feedback	Healthy adult volunteers, mean age 30, n = 32	Electronic instrument that measures continuously the movement of a slider connected to a computer with a continuous range response varying from 0-10	Test-re-test reliability reported as "excellent" but no statistics were given	Considered valid by authors, no discussion of testing for validity	Required a sophisticated computer software and hardware assembly; no validity reported	2b

Instrument Reference	Framework	Sample Subjects	Instrument Description and Scoring	Reliability	Validity	Feasibility	Level of Evidence[58]
Multidimensional Affect and Pain Survey (MAPS): [60]	Frequency pattern of correlations	Oncology patients at one major medical center with various types of cancer, n = 81	101 item instrument describing pain and pain symptoms and patient rate agreement with descriptor on a 0-5 point scale; 0 = none at all, 5 = very much so	Not reported	Factor analysis using pattern analysis approach	101 questions is a significant burden on the respondent; over 70 minutes was required to complete the instrument; difficult to score	2b
Defense and Veterans Pain Rating Scale (DVPRS): [57]	Not reported	Military members (active duty or retired); n = 350	5-item VAS plus PFS with response categories 0-10 with 0=none and 10=worst combined with 4 supplemental questions with response categories 0-10 indicating degree of agreement with the statement	Internal consistency reliability Cronbach's alpha = 0.902	Principal component factor analysis for construct validity factor loadings >0.82	8-9th grade reading level; easy to administer and quick to answer, little burden on the participants, unknown about availability outside the military population; useful in clinical research	1b

Instrument Reference	Framework	Sample Subjects	Instrument Description and Scoring	Reliability	Validity	Feasibility	Level of Evidence[58]
Visual Analog Scale for Pain (VAS): [63]		Adult patients in the emergency room of two facilities, n = 96	1-item scale with response categories continuous along a 100mm line representing a continuum of pain levels; one end "least possible pain" other end "worst possible pain"	ICC were used with 0.97 ICCs between 1-minute measurements	Convergant validity when correlated with NPS 0.95	Simple, 1-item scale, usable for those not able to read, universal in language, widely used; useful in clinical research	1b
McGill Pain Questionnaire (MPQ): [64]	Not reported	Adult patients participating in larger RCT in VA medical system; n = 221	22-item pain descriptors including 4 summary scales assessing continuous, intermittent, descriptors, and affect with a 0-10 rating scale; 0=none, 1=worst possible	3 confirmatory factor analysis models used; reliability for 3 models are r = 0.98; r = 0.88; r = 0.86	Convergent validity as compared to itself r = 0.74; discriminant validity reported as "excellent" but without statistics	Widely used instrument that requires only 10 minutes to complete; comprehensive examination of pain; limited to English speaking/reading patients	1b

Figure 1. Search Results

Figure 1. Search Results
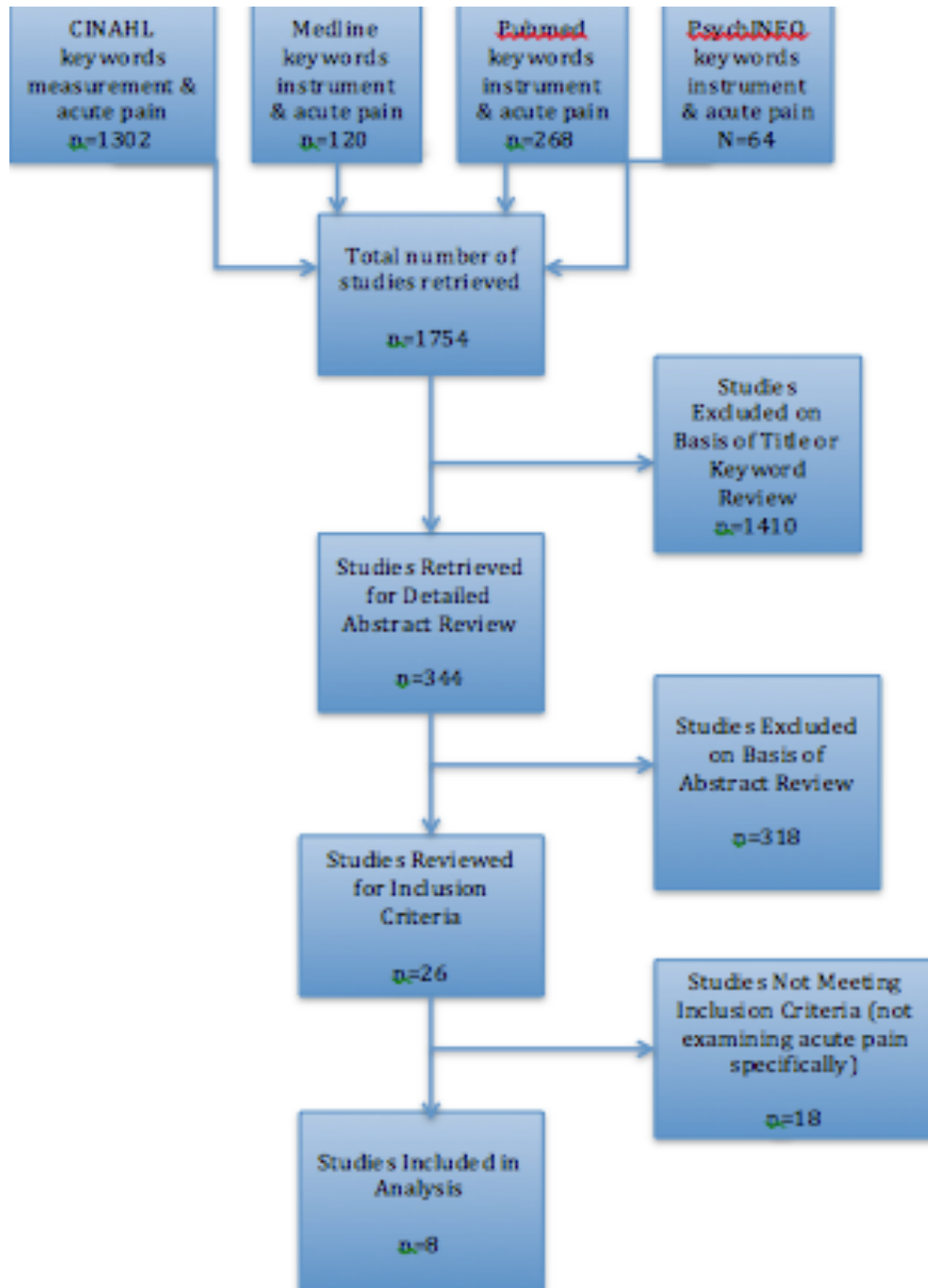
Chapter 4: Clinical utility of pharmacogenomic testing among anesthesia providers:

A mixed-method study

Introduction

Pharmacogenomic testing is becoming more widely used to assist healthcare providers make personalize healthcare decisions; however, a stark gap exists in the literature about the perceived clinical utility of pharmacogenomic testing in supporting prescriptive decision-making among practicing anesthesia providers. Pharmacogenomic testing can categorize how an individual's variation in deoxyribonucleic acid (DNA) will control drug metabolism by programming how the cytochrome P-450 (CYP450) system for drug metabolism functions.[5] With pharmacogenomic testing of an individual's CYP450 system, the results can support an anesthesia provider's prescriptive decision-making and help minimize 'guessing' about which drug and dose is best for the patient[69]. In the rapidly developing field of personalized medicine, in which pharmacogenomics play an integral part, this technology is a key component of helping an anesthesia provider determines which medications will work best for their patient.

Despite the advancement in pharmacogenomic testing technology and the supporting interpretative software translating its results, the clinical uptake has been slow.[1,5] Although clinical outcomes studies demonstrate superior patient outcomes when pharmacologic decisions are made based on genetic information, few studies demonstrate the perceived clinical utility of pharmacogenomic technology in supporting prescriptive decision-making.[6,69,70] Attitudes of anesthesia providers towards pharmacogenomic testing and their perceptions of clinical utility of the technology in supporting clinical decisions are currently unknown.

In the United States, there are multiple corporate entities that produce, market, and promote pharmacogenomic testing technology and the supporting software for interpretation of

the results. The myriad of differences in the complexity of the testing platforms, the availability of the technology in real-world clinical practice settings, and the ability of the patient and the anesthesia provider to interpret and apply the results in real-world clinical practice is unknown.

As the clinical utility of the pharmacogenomic testing among anesthesia providers is currently unknown, this study aimed at describing how anesthesia providers in clinical practice perceive the usefulness and support the uptake of pharmacogenomic testing as well as quantify these perceptions. Additionally, results of previous work demonstrate that both qualitative and quantitative measurement of provider perceptions of clinical utility is necessary before advancement of technology into routine clinical practice can be successful.[15] Similar work has been conducted in the field of hepatology, nutrition, and primary care with feasibility of a mixed-method approach to establishing clinical utility having been established in these previous works.[15,16,71] The purpose of this study, then, is to develop a survey based on qualitative perceptions of anesthesia providers to better understand the perceived clinical utility of pharmacogenomic testing related to clinical prescriptive decision-making.

Theoretical Framework

The guiding framework for this study is the Centers for Disease Control and Prevention's (CDC) ACCE Model of Public Health Genomics.[22] The model's dimensions include analytic validity; clinical validity; clinical utility; and ethical, legal, and social implications of a genetic test. The clinical utility portion, or outer ring, of the model was used to ground this mixed-method study (Figure 1). Anesthesia providers were questioned about knowledge, education, perceived barriers, and perceptions of how the technology could impact patient care.

Figure 1. CDC ACCE Model of Public Health Genomics

Research Design and Methodology

This study was a sequential qualitative-quantitative mixed-method design that explored

the perceptions of anesthesia providers regarding the clinical utility of pharmacogenomic testing.

Participants were any licensed practicing anesthesia provider with unrestricted privileges to

provide direct patient care. Ten individuals were recruited to participate in the qualitative phase

of this study. Initially, qualitative semi-structured interviews were conducted with 10 practicing

anesthesia providers. Following analysis of the qualitative data, probes were developed based on

the themes that emerged from the qualitative interviews. These probes were then formulated into

a quantitative survey designed to quantify the perceptions of anesthesia providers about clinical

utility of pharmacogenomic testing.

The qualitative portion of the study utilized case-study methodology as originally

proposed by Yin.[72] Using purposive sampling of 10 practicing anesthesia providers, semi-

structured interviews were conducted. Questions for the qualitative interview were developed

using the CDC ACCE Model of Public Health Genomics; Clinical Utility.[22] Appendix 1 is the

focused interview guide. Interviews were conducted in the anesthesia provider's place of business, usually in a private office or private consultation room. The primary investigator conducted all interviews, which were audio recorded and transcribed using a professional transcription service.

Following data analysis and thematic development of the qualitative data, probes for a quantitative survey were developed from the qualitative data set results. Survey development was based on the Office of Behavioral and Social Sciences and Research guidance on development of surveys in the field of human subjects research.[73] This survey was initially tested with the original 10 participants from the qualitative portion of the study. This allowed for triangulation of the data and revision of the initial survey instrument.[73] Cognitive pretesting and subsequent item revision were conducted. The final survey that was administered is attached as Appendix 2. The survey was constructed and administered using the REDCap ™ system. The sample for the quantitative survey was obtained from the American Association of Nurse Anesthetists (AANA) and consisted of a random sample of 3000 practicing Certified Registered Nurse Anesthetists (CRNA) in the United States and military instillations worldwide.[74] The survey was distributed electronically, in a blinded fashion, and the respondents could answer on a computer, smartphone, or tablet device.

Data Analysis

Qualitative data analysis was conducted using case-study methodology as proposed by Yin and colleagues.[72] Following professional transcription, the individual interview transcripts were validated for quality by the primary investigator. Using multiple-embedded case study methodology, each provider was assumed to represent an individual case. Each anesthesia provider represents an individual case because they each care for a cadre of patients; their

individual practice represents the sum of the care provided for the cadre of individuals receiving an intervention.[72,75] Yin indicates that for case-study methodology exploring new concepts, only a minimum number of subjects are necessary to achieve data saturation.

Using NVivo® qualitative data analysis software, data were first deductively coded, framed by the CDC ACCE Model of Clinical Utility.[22] Using cross-case synthesis methods, each anesthesia provider was treated as a separate case and embedded cases were established after the first case was coded. Following deductive coding, inductive coding using constant comparison was used to develop key themes in the entire data set.[76] The process used to establish rigor of the findings was based on a systematic process of coding and interpretation.[77] In this process, the primary investigator initially reviewed and coded the data based on the ACCE Model. Next, a second, expert qualitative researcher coded the data using the same method. Systematic comparison was made between the primary investigator and the expert methodologist to compare findings, negotiate consensus, and ensure rigor of the coding and analysis process.[77]

Following qualitative data analysis, the themes that emerged were used to formulate survey items aimed at quantifying provider perceptions of clinical utility. Initially, questions were constructed based upon each theme that emerged and those questions underwent cognitive pretesting with the group of 10 original participants. Refinement of the questions was then conducted. Each question consisted of a unidirectional, Likert-scale type question that aimed to measure only one distinct concept. Two items were constructed per theme for a total of 14-items on the final survey.

Factor analysis using the maximum likelihood extraction was used to analyze the data.[78] This method allows for inferences to be made on the population as a whole based on the extracted factors from the sample, which is appropriate for this quantitative data.[79,80] Because

the factor analysis is exploratory and descriptive, an assumption of the maximum likelihood method that each item have a normal distribution was relaxed. To determine the strength of relationship among items as a measure of sampling adequacy the Kaiser-Meyer-Olkin test was used to evaluate whether the numbers of significant correlations were sufficient for factor analysis.[79] Criteria for extraction included visual examination of the Scree plot and as a secondary measure, Kaiser's criteria recommending retention of factors with eigenvalues greater than 1.[79] To facilitate factor interpretation, factors were rotated using the Direct Oblimin technique, which is useful when factors are thought to be related. Following maximum likelihood extraction, Horn's parallel analysis was carried out to confirm the number of factors extracted sufficiently loaded and that minimal residual remained. Data were analyzed using IBM SPSS version 22 for Mac (IBM Corp, Armonk, New York).

Qualitative Results

Deductive coding was conducted first. Framed by the CDC ACCE Model of Public Health Genomics, five themes emerged from the analyzed data set. These themes were: a lack of understanding and knowledge about the technology, a lack of facilities to conduct and interpret the testing, limited access to the technology, economic concerns about genetic testing, and finally legal and ethical implications of ordering genetic testing.

The first theme that emerged from the data centered on understanding and knowledge about pharmacogenomic testing and the interpretation of the results related to clinical decisions. Providers indicated they did not have enough education as it relates to pharmacogenomic testing to see it as useful in their anesthesia practice:

> *"Well, I'm not really sure how it would impact the patients because I don't yet know the value of it, I don't know enough about it."*

> *"We're gaining knowledge that may have utility once we understand it better"*

Further, providers indicated they lacked facilities to conduct and interpret the findings of pharmacogenomic testing. Most providers indicated that they did not have access to ordering the pharmacogenomic test in their facility of practice nor did they know how to order the test if it was available. In answering the question regarding impactfulness of the technology, providers indicated they were limited at times in their access to the technology:

> *"I guess coming from a rural-type facility and practice, we're limited a lot of times in things that are available to us. We may not have a big variety of medications to choose from. We tend to be pretty limited to what we have and so, in some ways, it may not influence what we do."*

> *"Currently I'm in a small facility and in a rural facility and it seems like, with medicine, that technology is usually centered around the big facilities where they've got the money and they've got the ability to study those technologies"*

Anesthesia providers universally were concerned about the economic implications of pharmacogenomic testing. Concerns related to the actual cost to the patient, cost to the healthcare system as a whole, and costs to the provider if the third-party payers do not cover the testing expense were all prominent in the data. Additionally, providers thought that there is probably not a good cost-benefit ratio that is currently available to support the use of pharmacogenomic testing in their practice:

> *"Did I really need to do an expensive test to figure that out? Or, can I just write a prescription and if they responded really well to it, okay, break in half-- take a half one, instead. Or, "Wow, that isn't strong enough for you? Okay, well, you have to take two instead of one." I didn't need a multi-thousand dollar test to figure that out"*

> *"I think actual barriers may be to some degree the expense of it as it's being developed. I think any new technology is usually pretty expensive, until it has been in use for a longer period of time. I think that that's the main problem, is going to be money"*

> *"I think instituting the technology is going to be somewhat slow. I think people are really resistant to changing things in the first place. It's expensive, I'm sure, to develop this technology, and I think that those kinds of things can make an adoption of a technology like that somewhat difficult"*

"If the technology advances, it will have to come to a point where it became affordable which takes time and then it may have an impact on rural facilities."

Anesthesia providers did seem to think that pharmacogenomic testing might be advantageous which speaks to the effective benefit of the ACCE Model. Participants expressed the results of pharmacogenomic testing could be useful to plan their anesthetic care. They expressed pharmacogenomic testing would result in less pain, faster recovery times, and provide a better, more patient-centered way of delivering anesthesia care. Providers indicated they think the technology would help to focus care, inform decisions, and have positive impacts on patient outcomes.

"I think the advantages to the technology is being able to narrow down with our patients what is the best drug to be used for them - the amounts of the drug. So, that we can target our patient population to tailor the best anesthetic for them"

"If you could really tailor your anesthetic to that patient then obviously you're going to wake up faster, you're going to wake up crisper, you're going to wake up the patient more alert, less pain and all the side effects that go along with what we do in the OR so that they would have a better experience with that"

The final theme that emerged from the deductive analysis of the data focused on the ethical, legal, and social implications of using pharmacogenomic testing to help inform clinical decisions. Providers generally expressed that there was perhaps an increased liability or exposure to risk if they ordered and used a genetic test in practice:

"I think if I do the test and it shows, on one side, they might be have a very high addictive potential and I decide to prescribe anyway, that might increase my liability. Because, I knew ahead of time this was going to be a problem. On the other side, if it shows that they were a high metabolizer and they would require high doses of opioid, and so, I used that to drive my prescribing practices, in that I would write higher doses for them right off the bat. And, they either had an adverse event based on the higher dose that I gave them, and/or they were diverting and I just thought, Oh well, I misinterpreted that information as they are high metabolizers, so, I'm just going to have to keep on giving them more and more medications. I think that might be misleading or a false sense of security."

Following the deductive coding, inductive coding was undertaken using constant comparison methods. The first theme that emerged from the inductive coding was the complexity of the technology. Providers general thought that the pharmacogenomic testing was extremely complex and difficult to understand. They indicated not only was the technology complex in interpretation, but understanding when it was indicated an how to go about ordering a test, as well as developing their personal comfort in using the test in clinical practice was all very confusing:

> *"All of the details of that are very confusing to me. It's not something I am comfortable with and it's almost to the extent that I perceive the interpretation of the test as something that would be so burdensome that I wouldn't want to do it."*

> *"I think, from my perception, is that we have a test that may or may not be a really powerful tool. And, the deal is that they've got a billing code for it, but there is not a lot of research out there to show us if you do this test in this scenario it can improve your outcomes in this fashion."*

The final theme was the providers' feelings that using the pharmacogenomic testing to support decision-making would help them avoid complications in the care of their patients. Providers felt that they could use the technology to narrow and focus their care and make decisions about the very best care possible; not just the status quo. Additionally, they felt that knowledge was power and the more information you know ahead of the proposed anesthetic the better the care delivered:

> *"My initial inclination would be that if you've got insight into the genetics of a person that that would dictate decisions that you make for them, along the lines of malignant hyperthermia or something like that. The more you know about the makeup of the person, the better able you are to choose appropriate medications."*

> *"I think the advantages to the technology is being able to narrow down with our patients what is the best drug to be used for them - the amounts of the drug. So, that we can target our patient population to tailor the best anesthetic for them"*

> *"Less post-operative nausea, and vomiting, etc. Those kinds of things. Less post-operative pain. I really think that that has a whole lot of promise for patients."*

Quantitative Analysis

Following analysis of the qualitative data, seven themes emerged as concerns anesthesia providers had regarding pharmacogenomic testing. To accomplish factor analysis of the proposed instrument, two items were constructed per construct to be measured. The primary investigator developed the 14-item survey and cognitive pre-testing of the survey was accomplished with all ten of the qualitative participants. These qualitative participants practiced in community hospitals, rural hospitals, outpatient settings, and academic medical centers. Their years of experience ranged from six to 27 and all were actively practicing anesthesia providers. Following refinement of the survey instrument, it was formatted into the REDCap ™ survey management system. Survey items consisted of 14 items on a 0-10 Likert scale with 0 meaning completely disagree and 10 meaning completely agree. All items were written with unidirectionality.

A random sample of 6,000 practicing Certified Registered Nurse Anesthetists in the United States and military instillations worldwide were invited to participate in the electronic survey. Through the AANA research division, a random list of potential participants was formulated. This list was generated from the database of CRNAs and filters were applied to only sample actively practicing CRNAs. An invitation letter was electronically distributed to participants explaining the purpose of the survey and inviting participation. An electronic link was included in the letter directing potential participants to the electronic survey system. A total of 325 surveys were returned representing a 5% response rate.

Construct validity was assessed by factor analysis. A total of 262 complete surveys were used in the analysis and cases were excluded list wise if they had any missing variable responses.

Results

Participant characteristics

The age of the participants was a mean of 48 +/- 11 years. There were 44% male and

52% female respondents. Seventy eight percent of the respondents did not identify a practicing

specialization while 1% indicated they specialized in neuro anesthesia, 4% in obstetrical

anesthesia, and 5% in pediatric anesthesia. Fifty four percent of respondents indicated they

practiced in a community hospital, 25% in an academic medical center, and 15% in outpatient

settings. Seventy two percent of the respondents reported a Master's degree as their highest

earned degree with 12% Bachelor's, 8% Doctorate, and 6% Certificate-prepared. Participant

characteristics are presented in Table 1.

Table 1. Participant characteristics.

Age (years)	48 +/- 11
Gender (% male)	44
Practice location (%)	
-community hospital	54
-academic medical center	25
-outpatient facility	15
Practice type (%)	
-not specialized	78
-pediatrics	5
-OB	4
-neuro	1
Degree (%)	
-Certificate	6
-Bachelor's	12
-Master's	72
-Doctorate	8

Factor Analysis

The Kaiser-Meyer-Olkin test (KMO), an overall measure of sampling adequacy, had a

value of 0.850 which indicated the patterns of correlations were relatively compact and sufficient

to reveal distinct and reliable factors.[79] Factor analysis resulted in three factors. Following

maximum likelihood extraction, Horn's parallel analysis was carried out to confirm the number

of factors extracted. Parallel analysis confirmed that three factors sufficiently loaded and

minimal residual remained. Following analyses, the pattern matrix was examined to determine

the unique contribution of each item to each factor. Total variance is presented in Table 2 and

items that loaded on each factor are presented in Table 3.

Table 2. Total variance explained

Total Variance Explained

Factor	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings[a]
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	4.844	34.597	34.597	4.341	31.009	31.009	3.597
2	2.057	14.696	49.292	1.586	11.331	42.340	2.940
3	1.228	8.773	58.065	.716	5.115	47.455	3.035
4	.990	7.069	65.134				
5	.810	5.786	70.921				
6	.780	5.575	76.495				
7	.565	4.037	80.532				
8	.527	3.767	84.300				
9	.491	3.509	87.809				
10	.408	2.913	90.722				
11	.383	2.738	93.460				
12	.353	2.523	95.983				
13	.297	2.124	98.107				
14	.265	1.893	100.000				

Extraction Method: Maximum Likelihood.
a. When factors are correlated, sums of squared loadings cannot be added to obtain a total variance.

The pattern matrix was examined to examine the unique contributions to each factor.

Items that loaded on each factor are presented in Table 3.

Table 3. Rotated factor loadings

Items	Factor 1 (benefit)	Factor 2 (knowledge)	Factor 3 (concerns)
Tailored care	.879		
Quicker wakeup & less pain	.808		
Reduce adverse drug events	.741		
Perceived benefit	.467		
Comfort with testing		.803	
Enough knowledge to use		.753	
Specific training on testing		.576	
Way to order		.498	
Easy to use		.462	
Location uses testing		.439	
Cost prohibitive			.932
Cost is reason not used			.629
Testing means more liability			.496
Ethical concerns about testing			.400

Maximum likelihood extraction pattern matrix with Oblimin rotation. Only related items with loadings greater than 0.4 are shown.

Factor 1 was labeled "benefit" because items related to the perceived "benefit" of the pharmacogenomic test loaded on this factor. Factor 2 was labeled "knowledge" because items related to understanding the technology and interpretation of the test results loaded on this factor. Factor 3 was labeled "concerns" because items related to liability, cost, and ethical considerations of pharmacogenomic testing loaded on this factor. The means for the scores for each item that loaded onto each factor are presented in Table 4.

Table 4. Means (standard deviation) of items loaded onto each factor.

Item	Mean (Standard deviation)
Factor One (Benefit)	
Pharmacogenomic testing would allow me to tailor my anesthetic to my patients	4.6 (3.3)
If I used pharmacogenomic testing, my patients would wake up quicker and in less pain.	3.4 (2.9)
By using pharmacogenomic testing, I would reduce adverse drug events.	4.4 (3.3)
I know how pharmacogenomic testing would benefit my patients.	3.9 (3.0)
Factor Two (knowledge)	
I am confortable interpreting the results of a pharmacogenomic test	1.2 (2.1)
I have enough knowledge to use pharmacogenomic testing to help me make clinical decisions	1.2 (2.1)
I have received some form of training in the use of pharmacogenomic testing as it relates to making clinical decisions	1.6 (2.4)
In my primary practice location, I have access to or can order pharmacogenomic testing	0.6 (1.4)
Pharmacogenomic testing easy to use an interpret	2.1 (2.4)
My primary practice location uses pharmacogenomic testing to help providers make clinical decisions	0.7 (1.5)
Factor Three (concerns)	
Pharmacogenomic testing is cost prohibitive	4.1 (3.1)
The reason pharmacogenomic testing is not widely used is cost	4.2 (3.4)
If I use pharmacogenomic testing in my practice, I am taking on additional liability	2.8 (2.9)
I have concerns about the ethical aspects of pharmacogenomic testing	2.8 (2.9)

Discussion and Conclusions

The use of pharmacogenomic technology to support prescriptive decision-making among anesthesia providers has not been established. Qualitative data shows providers expressed they lack the knowledge necessary to use pharmacogenomic testing in clinical practice. Also, these providers expressed that cost and ethical/legal implications of pharmacogenomic testing might prohibit them from incorporating this modality in their anesthesia practice. Anesthesia providers expressed that the technology is complex and extremely difficult to understand; further, they often do not have access to the technology or the ability to order the test in the place of practice.

Anesthesia providers indicated that pharmacogenomic testing is promising and using it could result in better, more patient-centered anesthesia care. This is an interesting finding, as the anesthesia provider seems to understand the basic premise behind pharmacogenomics; however, they have stated they lack the knowledge necessary to actually use and interpret the findings of a pharmacogenomic test. Providers generally indicated that more personalized prescriptive decisions could be made, especially for acute pain and nausea prevention, if pharmacogenomic testing is used in anesthesia practice. Along with providing more personalized care, anesthesia providers do indicate that pharmacogenomic testing would help to reduce adverse drug events and overall help to reduce poor outcomes in clinical practice.

Results of the factor analysis of the quantitative survey show that anesthesia providers' use of pharmacogenomic testing can help to be explained by three phenomena: lack of knowledge, economic and ethical/legal concerns, and perceived or anticipated benefit to the patient. Items from a 14-item survey can be effectively reduced to fewer items that would directly question these 3 phenomena.

Limitations exist in this study. First, the qualitative interviews were conducted with anesthesia providers that were geographically located in one region of North Texas. These interviews and their resulting data do not represent the anesthesia population as a whole. Although saturation was reached in the qualitative analysis, additional interviews could have shown additional themes and feelings about pharmacogenomic testing. Second, a very small response rate on the quantitative survey could have biased the results. The title of the survey might have dissuaded individuals from responding, as pharmacogenomics is a foreign concept to many practicing anesthesia providers.

Future work should include analysis of the results of each item in the survey along with correlational analyses to help determine if there are predictive factors that might play into an individual provider's perceptions and knowledge about pharmacogenomic testing (such as age, degree, practice location).

Importantly, from this study, it was discovered that anesthesia providers need additional education about pharmacogenomic testing. Providers are unaware of the rather minimal cost of the testing and the wide availability of testing through various commercial entities. Providers are also unaware of the specific outcome studies that demonstrate superiority in pain control and antiemetic therapy when pharmacogenomic testing is used to guide prescriptive decision-making. Additional education in the areas ethical and legal implications of pharmacogenomic testing as compared to a wider, more generalized genetic panel is needed. Interventions aimed at helping anesthesia providers understand pharmacogenomic testing, it's utility, use, and cost is necessary.

Funding:

Chapter 5: Summary and Conclusions

Synthesis

The three manuscripts of this dissertation explore the field of genetics and genetic testing as it relates to clinical practice. The literature has demonstrated that the era of personalized medicine is here and healthcare providers need to embrace the field of genetics as part of a comprehensive approach to providing healthcare. Despite the myriad of outcomes studies demonstrating how genetics and genetic testing can improve care, it remains a relatively foreign idea to most clinicians.

An analysis of the concept of genetic predisposition (Chapter 2) shows that it remains a relatively immature concept. The concept is seen differently by different groups of people which seems to indicate we are all "speaking a different language" when it comes to talking about genetics. Genetics can represent hope and insight to some while is represents risk and threats to others. To healthcare providers, the concept of genetic predisposition overlaps with other diagnostic and prognostic testing modalities in stratifying risk, determining treatment, and offering statistical insight for patients when speak about disease prognosis. The concept of genetics as predictive is not extremely clear in the literature and this research identifies the need to further clarify the concept of genetic predisposition for the patient and the healthcare provider alike.

In relation to this dissertation, the concept analysis of genetic predisposition demonstrates that the concept has no meaning to the anesthesia provider. Chapter 2 demonstrates a complete lack of literature in the area of anesthesia providers and understanding of genetic predisposition. Chapter 2 helps to define the research question as it relates to understand the concept of pharmacogenomic testing (one aspect of genetic predisposition) among anesthesia providers.

The concept of genetic predisposition, as it relates to helping predict drug responsiveness, is lacking in context, maturity, and formality among anesthesia providers.

In order to know if a treatment, therapy, or intervention is helpful, it is necessary to have psychometrically sound instruments to measure outcomes. The second manuscript (Chapter 3) is an integrative review of the literature about instruments to measure acute pain. This review identifies that pain is very difficult to measure because it is completely subjective. Furthermore, it was demonstrated that pain is multifactorial in nature and there is not one single physiological or biomarker that help to identify pain. This review does demonstrate that there are several instruments in current clinical use that have strong psychometric properties to measure acute pain. As anesthesia provider consider the use of pharmacogenomic testing to help make decisions regarding pain therapy, the need to psychometrically sound, clinically useful instruments to measure outcomes is critical.

The third manuscript (Chapter 4) of this dissertation explores the perceived clinical utility of pharmacogenomic testing to support clinical decision making among anesthesia providers. This mixed-method, sequential qualitative quantitative study used case study methodology to explore the perceptions of 10 anesthesia providers of pharmacogenomic testing. Using focused semi-structured interviews and multiple embedded case study analysis, it was determined that seven themes resonate with anesthesia providers related to pharmacogenomic testing. Using this foundational data, a quantitative survey was constructed to begin to develop a quantitative method of measuring perceived clinical utility of pharmacogenomic testing. This survey was electronically distributed and analysis was conducted using factor analysis.

The third manuscript helps to fill the gap in the literature that exists regarding anesthesia provider perceptions of pharmacogenomic testing. Results of this study shoe that anesthesia

providers have a lack of knowledge about how and when to use pharmacogenomic testing. Additionally, anesthesia providers have concerns about the ethical and legal implications of using genetic testing to help predict drug responses. Although anesthesia providers were shown to perceive benefits in using pharmacogenomic testing, their lack of knowledge about it's use and concerns about ethics and economics severely limits it's clinical utility.

The limitations of this dissertation involve the limited and focused population. As preliminary data concerning anesthesia providers only, inferences to other members of the healthcare community cannot be made. Additionally, this data is only preliminary and should be considered as pilot data. Further refinement of the proposed instrument is necessary to more precisely measure clinical utility of pharmacogenomic testing among anesthesia providers. Future directions include the development of a more robust instrument designed to measure clinical utility of pharmacogenomic testing among anesthesia providers. Also, the development of an intervention aimed at increasing anesthesia provider knowledge about pharmacogenomic testing is necessary.

Appendix 1: Focused Interview Guide:

1. What do you perceive as the advantages to this technology?

2. What do you perceive as potential or actual barriers to this technology?

3. How would this technology impact your patients?

4. How would this technology impact your practice?

5. In what ways are/would you anticipate using this technology in your practice?

6. What other information would you like to share about your potential use of this technology?

Appendix 2. Survey instrument.

Pharmacogenomic Survey

The purpose of this study is to better understand how Nurse Anesthetists perceive pharmacogenomic testing. This study is voluntary and you may withdraw at any point. It should take no more than 5 minutes to complee this study.

The data collected in this study is part of a PhD Dissertation conducted by Dru Riddle, CRNA, DNP under the mentorship of Mat Gregoski, PhD, MS, Chair. The survey has been approved by the Medical Univeristy of South Carolina IRB Number Pro0037344

Your completion of this survey is apprecaited!

1) What is your age in years?   _____

2) What is your gender?   ☐ Male
                                                 ☐ Female
                                                 ☐ Would prefer not to disclose

3) How many years have you been practicing anesthesia?   _____

4) What is the ZIP code of your primary practice   _____
   location?

5) What is your primary clinical area?   ☐ Community hospital
                                                 ☐ Academic medical center
                                                 ☐ Outpatient surgery/endoscopy/pain center
                                                 ☐ Office-based anesthesia
                                                 ☐ Administration

6) What is your primary area of specialization? ☐ Not specialized
                                                 ☐ Neuro
                                                 ☐ OB
                                                 ☐ Pediatrics
                                                 ☐ Orthopedics
                                                 ☐ Cardiac
                                                 ☐ Pain management
                                                 ☐ Other (not listed above)

7) What is your highest academic degree completed?   ☐ Certificate
                                                 ☐ Bachelor's
                                                 ☐ Master's
                                                 ☐ Doctorate

In the next part, you will be presented with a series a statements on a scale of 0-10, where 0= completely disagree and 10=completely agree

		0	1	2	3	4	5	6	7	8	9	10
8)	I know how pharmacogenomic testing would benefit my patients.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9)	Pharmacogenomic testing is cost prohibitive.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10)	I have received some form of training in the use of pharmacogenomic testing as it relates to making clinical decisions.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11)	My primary practice location uses pharmacogenomic testing to help providers make clinical decisions.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12)	By using pharmacogenomic testing, I would reduce adverse drug events.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13)	The reason pharmacogenomic testing is not used widely is cost.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14)	If I used pharmacogenomic testing, my patients would wake up quicker and in less pain.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
15)	I have concerns about the ethical aspects of pharmacogenomic testing.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
16)	Pharmacogenomic testing would allow me to tailor my anesthetic to my patients.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17)	I am confortable interpreting the results of a pharmacogenomic test.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
18)	In my primary practice location, I have access to or can order pharmacogenomic testing.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19)	Pharmacogenomic testing is easy to understand and use.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
20)	If I use pharmacogenomic testing in my practice, I am taking on additional liability.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21)	I have enough knowledge to use pharmacogenomic testing to help me make clinical decisions.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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