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COMMUNITY-BASED PARTICIPATORY RESEARCH TO PARTNER WITH THE  
CONFEDERATED SALISH AND KOOTENAI TRIBES IN PHARMACOGENETICS  
RESEARCH

By

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B.S. Human Biological Sciences, University of Montana, Missoula, MT, 2010

Thesis

presented in partial fulfillment of the requirements  
for the degree of

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Pharmaceutical Sciences

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## Community-Based Participatory Research to Partner with the Confederated Salish and Kootenai Tribes in Pharmacogenetics Research

Chairperson: Dr. Erica L. Woodahl

Pharmacogenetics research has advanced our knowledge of the genetic basis of individual drug responses. The aim of pharmacogenetics research is to provide opportunities for the development of strategies aimed at discovering clinically relevant gene-drug pairs. Further benefits stem from the translation of pharmacogenetics research into the clinic to identify patients who are at high risk of adverse drug events. However, American Indian and Alaska Native (AI/AN) populations have not benefited markedly from genetics-guided therapeutics. A key strategy in engaging AI/AN people in pharmacogenetics research has been the implementation of community-based participatory research (CBPR). CBPR is a qualitative research methodology in which a partnership is formed between the research institution and the community under study. CBPR provides a framework for both partners to be involved in all aspects of the research process, from developing research questions to data analysis, and dissemination of research findings.

Early in the project, approval was given by the Confederated Salish and Kootenai Tribes (CSKT) through discussions with Tribal Health and Tribal Council to conduct pharmacogenetics research with the CSKT community. Thereafter, a collaborative university-community partnership was established with the CSKT to ensure the community has sufficient knowledge about pharmacogenetics research and to develop culturally-relevant research strategies. We formed an oversight committee, the Community Pharmacogenetics Advisory Council (CPAC), to ensure community involvement. We also held workshops to provide education and bring awareness to the community about pharmacogenetics research. CPAC engagement and education through workshops and research involvement was evaluated through a questionnaire. Seventeen healthcare provider interviews have been conducted, transcribed, and analyzed. The interviews were conducted with Montana healthcare providers to assess their views on the potential benefits and harms of pharmacogenetics research and the feasibility of its future implementation into Tribal Health. In addition, two focus groups have been conducted thus far. CPAC helped design a moderator's guide and developed recruitment tools for focus groups. These focus group materials were used and will continue to be used to conduct focus groups with enrolled CSKT members who receive their healthcare through Tribal Health to assess their views and perceptions of pharmacogenetics research, its translation into the clinic, and dissemination of results to the broader community. The details of the results of the focus groups and healthcare provider interviews will be described in this study.

This collaboration created a CBPR framework that best fits the needs of the community. Engaging CSKT community partners in informal and formal discussions about pharmacogenetics research has aided in identifying priorities of the community and building mutually productive partnerships

# TABLE OF CONTENTS

	Page
List of Tables .....	iv
Chapter 1: Introduction .....	1
1.1. Pharmacogenetics.....	3
1.1.1. Knowledge-Based Systems for Pharmacogenetic Testing .....	5
1.1.2. Views of Healthcare Providers on Pharmacogenetics.....	9
1.1.3. Views of Patients on Pharmacogenetics.....	10
1.2. Community-Based Participatory Research.....	12
1.2.1. Community-Based Participatory Research in Healthcare ....	15
1.2.2. Community-Based Participatory Research with AI/AN Communities .....	16
1.3. Specific Aims.....	17
Chapter 2: Community-Based Participatory Research to Facilitate Community Involvement and Engagement with Confederated Salish and Kootenai Tribal Members.	21
2.1. Introduction .....	22
2.2. Methods.....	25
2.2.1. Establishment of Research Partnership .....	25
2.2.2. Formation of Community Pharmacogenetics Advisory Council .....	26

2.2.3.	Capacity and Community Engagement .....	27
2.2.4.	Development of Focus Group Materials .....	29
2.3.	Results .....	29
2.3.1.	Community Pharmacogenetics Advisory Council .....	29
2.3.2.	Genetics Education for Native American Workshop .....	31
2.3.3.	nDigidreams Digital Storytelling .....	31
2.3.4.	Focus Group Materials.....	32
2.4.	Discussion .....	33
Chapter 3:	Healthcare Provider Views on Pharmacogenetics Research and its Future Implementation into the Confederated Salish and Kootenai Tribal Health Clinics.....	41
3.1	Introduction.....	42
3.2.	Methods .....	43
3.2.1.	Study Subjects .....	44
3.2.2.	Healthcare Provider Interviews .....	44
3.2.3.	Qualitative Analysis.....	45
3.3.	Results .....	45
3.3.1.	Healthcare Provider Interview Analysis .....	45
3.4.	Discussion.....	63
Chapter 4:	Patients' Views of Pharmacogenetics Research Amongst the Confederated Salish and Kootenai Tribes .....	66

4.1. Introduction .....	67
4.2 Methods.....	69
4.2.1. Study Subjects.....	69
4.2.2. Focus Groups .....	69
4.2.3. Qualitative Analysis .....	70
4.3. Results.....	71
4.3.1. Focus Group Summary .....	71
4.3.2. Field of Pharmacogenetics Research.....	71
4.3.3. Clinical Utility of Pharmacogenetic Tests.....	74
4.3.4. Dissemination of Results .....	75
4.4. Discussion .....	75
Chapter 5: Conclusions .....	78
Bibliography.....	85

## LIST OF TABLES

Table Number	Page
1.1. Clinically Relevant Drug Metabolizing Enzymes .....	19
1.2. Product Labeling: Available Pharmacogenetic Tests .....	20
2.1. Capacity Building and Community Involvement Action Activities.....	38
2.2. Education Objectives from GENA® Workshop .....	39
2.3. Examples of Moderator’s Guide Questions for Focus Groups.....	40



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## **DEDICATION**

To my family, Manuel, Cheryl, Joshalyn, Carmen, Carlos, Julia, Keegan, Caleb, and Wesley. Their love and support encourage my success.

## CHAPTER 1

### INTRODUCTION

Personalized medicine offers the opportunity to improve drug responses and patient outcomes by tailoring the way healthcare is provided to an individual. The most common approach in administering drugs is to start with a standardized dosing regimen. Unfortunately people have variable drug responses, some exhibit undesirable or toxic effects, and others may not experience any therapeutic effects at all when given a standard dose of drug. Many factors contribute to interindividual variation including age, sex, diet, environmental factors, drug interactions, liver and renal function, and concomitant diseases. It is recognized that interindividual differences are also influenced by genetic variation which leads to individual differences in drug disposition (i.e., drug absorption, distribution, metabolism, and elimination, or ADME), efficacy, and toxicity. Depending on the drug, genetics can contribute to anywhere from 15% to 95% of variation in patient drug response (Eichelbaum et al., 2006).

Genetic variation has been understood for several decades, and the concept that testing for genetic variation might be used to guide drug therapy dates back to the late 1950s where patients who inherited an enzyme deficiency were unable to metabolize anti-malarial primaquine and therefore experienced severe hemolysis (Eichelbaum, 2006 and Beutler, 1969). Later in the 1980s, researchers identified a drug metabolizing enzyme cytochrome P450 (CYP450) gene (*CYP2D6*) polymorphism and its role in the metabolism of numerous drugs targeting the central nervous system and cardiovascular system (Evans and Relling 1999). These discoveries have markedly contributed to increased interests in genome mapping and sequencing; as a result an array of genotypes have been identified in key drug metabolizing enzymes and shown to play a role in variation of clinical patient outcomes. To this end, huge efforts in genetics research have

targeted CYP450 drug metabolizing enzymes due to their polymorphic nature and their roles in phase I drug metabolism. Phase I drug metabolism results in more polar metabolites of drugs through oxidation, reduction, and hydrolysis which allows them to be more readily excreted. In addition, phase I drug metabolism can also lead to either activation or inactivation of pharmaceuticals and therefore influence their bioavailability (Evans and Relling 1999; Eichelbaum et al., 2006). This highlights the clinical significance of genetic variations in CYP450 enzymes that contribute largely to drug metabolism. In addition, genetic variation in drug transporters and drug targets has also been observed and shown to have clinical significance (Gardiner and Begg 2006). Investigating genetic variation in CYP450 enzymes, drug transporters, and drug targets offer opportunities to identify potentially important therapeutic effects on drug response.

In the following section, I will provide background information regarding pharmacogenetics research and its role in personalized medicine thus far. Next, I will address the reasons why pharmacogenetics research with American Indian and Alaska Native (AI/AN) populations has been limited. Furthermore, I will describe current healthcare provider and community views towards pharmacogenetics and its translation into the clinic. Finally, I will introduce community-based participatory research (CBPR) as an effective model in conducting successful pharmacogenetics research with AI/AN populations. This introductory chapter will conclude with discussion of future work in this area of research and the specific aims of my thesis.

## 1.1 PHARMACOGENETICS

Major discoveries of genetic factors that have proven to influence drug response

have provided compelling evidence of the potential to personalize medicine and has developed into a discipline, termed pharmacogenetics (Evans and Relling 1999). Pharmacogenetics involves genetics-related variations in drug metabolizing enzymes, drug transporters, and drug targets and how specific genotypes elicit a drug-related phenotypic response such as efficacy or toxicity (Crews et al., 2012). Individuals whose genotype is known can then be further classified into a phenotype. This phenotype is based on an individual's ability to metabolize a drug and is categorized as follows: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultra-rapid metabolizer (UM). There can be a number of genetic changes that can be associated with the same phenotype. In addition, the frequency of these genetic changes can be quite different among ethnic groups. The Food and Drug Administration (FDA) has incorporated pharmacogenetics that involves population studies with Europeans, African Americans, and Asian-American evaluating medications that cover 19 therapeutic areas with an emphasis in the areas of psychiatry, oncology, and cardiovascular diseases. The FDA has provided genetic labeling for over 113 drugs that include information about drug exposure and response variability, risk for adverse drug interactions, genotype-specific dosing, and mechanisms of action of drugs (Food and Drug Administration 2013). For example, the FDA has added to the labeling of codeine to recommend testing for patients to identify those with *CYP2D6* gene that encodes for a UM phenotype (Crews et al., 2012). *CYP2D6* is the primary enzyme that converts codeine into morphine (its active metabolite). This has severe implications in nursing mothers who take codeine and exhibit an UM phenotype resulting in increased morphine levels in their breast milk and increasing the risk of morphine overdose in their nursing infant (Koren et al., 2006). This

example highlights the potential benefits of pharmacogenetic testing in identifying patients who have a genotype that makes them more at risk for adverse drug reactions. Furthermore, this labeling information is made available for healthcare providers and patients. A partial list of clinically relevant pharmacogenetic examples is shown in Table 1.1. Some examples are genetic variation in drug metabolizing enzymes (CYP450s and thiopurine methyltransferase, TPMT), a drug transporter (organic anionic transporting protein, OATP1B1), and drug targets either for efficacy (vitamin K epoxide reductase, VKORC1,) or toxicity (HLA variants). However, further education and ease of accessibility to pharmacogenetics is still needed if there is to be successful implementation of this research into clinics. Fortunately, there are several resources available that are working to help facilitate the use of pharmacogenetic testing in clinical practice. The following section will discuss two of these resources and give examples of two drugs where pharmacogenetic testing has the ability to optimize treatment.

#### 1.1.1. KNOWLEDGE-BASED SYSTEMS FOR PHARMACOGENETIC TESTING

The goals of pharmacogenetic testing involve reliable interpretation of test results, availability of clinical guidelines for personalized dose regimens, and knowledge-based decision support systems (Crews et al., 2012). The International Tamoxifen Pharmacogenetic Consortium (ITPC) collects information from worldwide studies on genetic variants that are associated with tamoxifen metabolism and their effects on clinical outcomes of tamoxifen therapy. Tamoxifen is the standard of care treatment for estrogen receptor (ER)-positive breast cancer to help prevent recurrence of cancer. Tamoxifen (selective estrogen receptor modifier) therapy is important because breast

cancer is the most common disease affecting women in the U.S. with an estimated 232,340 new cases for the year 2013 (National Cancer Institute 2013). The therapeutic effects of tamoxifen are elicited through sequential bioactivation by phase I metabolism. Tamoxifen's metabolite, 4-hydroxytamoxifen had initially been identified as the main source of therapeutic efficacy due to its 100-fold higher affinity for estrogen receptors. However, evidence suggests that a secondary metabolite of tamoxifen, endoxifen, has receptor affinity similar to 4-hydroxytamoxifen and is the key source of therapeutic effects because its plasma concentrations are 10 times that of 4-hydroxytamoxifen. Furthermore, CYP2D6 is responsible for metabolism of tamoxifen into these active metabolites (Borges et al., 2006). Therefore, genetic variants of CYP2D6 that cause loss of function can result in increased risks of breast cancer recurrence due to lack of efficacy (Mürdter et al., 2011). These data encouraged the FDA to add labeling information that incorporated genetic factors and drug interactions between *CYP2D6* and tamoxifen treatment. Understanding the pharmacogenetics associated with tamoxifen can help clinicians choose a different therapy for ER-positive breast cancer patients (Goetz et al., 2008).

The Clinical Pharmacogenetics Implementation Consortium (CPIC), produces peer-reviewed guidelines for providers on the use of pharmacogenetic tests (Relling and Klein 2011). For example, CPIC has published guidelines for warfarin, also known as Coumadin, an anticoagulant agent used to treat and prevent thromboembolic disorders (Johnson et al., 2011). Over 2 million patients will be prescribed warfarin each year in the U.S. and of these patients, 20% will experience a severe bleeding event associated with overanticoagulation (Kitzmiller et al., 2011; Wysowski et al., 2007). Although a



commonly prescribed drug, there exist challenges in its management because it has a narrow therapeutic range and a wide interindividual variability. Risks associated with warfarin include bleeding or clotting events where patients who are prescribed too little medication will form dangerous blood clots, and those prescribed too much medication are at risk of severe bleeds (Rettie et al., 2006). In order to prevent such risks, warfarin is managed individually by measuring a patient's prothrombin time and monitoring their international normalized ratio (INR), a way to measure the state of coagulation. Sources of patient variability include: age, gender, weight, diet, drug interactions, disease-state, and ethnic background. In addition, genetic variation in the CYP2C9 drug metabolizing enzyme, the major pathway of warfarin metabolism and clearance, contributes to differences in warfarin dose requirements. Further studies have also identified a noncoding variant of another gene, the vitamin K epoxide reductase complex 1 (*VKORC1*) that lowers the expression of the warfarin target, vitamin K epoxide reductase protein, which results in warfarin sensitivity. (Johnson et al., 2011; Limdi et al., 2008; Higashi et al., 2002). This example illustrates the point that some cases will call for a comprehensive examination of more than one source of genetic liability for the same drug to explain a patient's drug response. In response to these genetic observations, the FDA has added prescribing guidelines to the administration of warfarin. These guidelines encourage healthcare providers to utilize genetic tests to improve warfarin dosing in individual patients. A list of currently available pharmacogenetic tests that have been incorporated in product labeling is depicted in Table 1.2.

The full promise of pharmacogenetic tests will emerge within the mainstream medical community by ensuring safety and efficacy of therapies particularly those with a

narrow therapeutic window (Fargher et al., 2007). In order for this to occur, inclusion of all ethnicities needs to be an added focus of pharmacogenetics research. There already exists evidence of interethnic differences in relation to variation in drug response. For example, in the case of midazolam and CYP3A5, it has been discovered that Caucasians express more of the nonfunctional gene as compared to African American populations and therefore dosage regimens will need to factor in population differences and tailor prescriptions appropriately (Lin et al., 2002; Kuehl et al., 2001; Lamba et al., 2002). Discoveries such as this highlight the value of including all world populations in pharmacogenetics research and so far pharmacogenetics studies have made efforts to include European, African American, Asian populations, with a few studies of genetic variation within indigenous populations in the Americas (Jaja et al., 2008; Fohner et al., 2013). However, a premise of this work is that beneficial pharmacogenetic testing should be accessible to all members of society, and therefore research is needed to address knowledge gaps related to the use of pharmacogenetics for American Indian and Alaska Native (AI/AN) populations in the United States. AI/AN populations are commonly understudied and therefore to ensure their inclusion in pharmacogenetics research, a partnership between the University of Montana and the Confederated Salish and Kootenai Tribes (CSKT) was established.

Pharmacogenetics represents a major component of the movement to “individualize medicine”, whereby determining which individuals will be responders, non-responders, or toxic responders to medications before treatment is the key to preventing adverse drug reactions. According to the FDA, in 2006 adverse drug reactions became the fourth leading cause of deaths in the U.S., thereby illustrating the importance

of pharmacogenetics in healthcare. However, in order for pharmacogenetics to reach beyond research and into the clinic, it is of value to explore people's views and understanding of this concept.

### 1.1.2. VIEWS OF HEALTHCARE PROVIDERS ON PHARMACOGENETICS

As the study of pharmacogenetics advances, there is a growing need to inform and prepare healthcare providers for the anticipated implementation of pharmacogenetics into the clinic. It is important to discuss strategies of how best to provide appropriate education, technical knowledge, and awareness to healthcare professionals for successful clinical translation and therefore views and perspectives from healthcare professionals is of value (Burke et al., 2002). Currently, there are few studies available that focus on views or opinions of healthcare professionals on this topic and it is for this reason that the clinical translation of pharmacogenetics has been difficult. One assumption is that there is a lack of knowledge on the side of clinicians that result in a resistance to change and clinical uptake of this technology that might benefit their patients (Hedgecoe, 2007). Another factor that plays a role is ethics, and clinicians who are familiar with pharmacogenetics and its benefits are still reluctant to adopt pharmacogenetic tests due to ethical concerns (i.e. privacy, misuse of specimens, potential harms) (Buchanan et al., 2002). A study was done to address and understand the root of these ethical concerns (Hedgecoe 2007). The focus of the study was discussing the use of apolipoprotein E (APOE) 4 allele testing which would determine whether a person would be a poor responder to the drug tacrine, used for the treatment of Alzheimer's disease. This pharmacogenetic link was first noted in 1995 and is a result that has been highly cited in

the realm of pharmacogenetics. However, APOE4 is also a susceptibility gene for Alzheimer's disease, and this fact has created opposition amongst the clinical community to use APOE4 testing due to ethical issues around disclosure of disease risk. One clinician explained, "that's the problem with the APOE4, it's not just a pharmacogenetic tool, it's also a risk factor for the disease" (Hedgecoe, 2007). Another study done by the National Health Service (NHS) National Genetics Education and Development Centre, had interviewed approximately 19 pharmacists about their views of pharmacogenetics (Newton et al., 2007). The general results were that the pharmacists did believe that pharmacogenetic testing could provide benefits in drug efficacy and safety, but there would first need to be evidence that explained clinical utility and cost-effectiveness. These benefits, however, could be enhanced if people have a better understanding of basic genetic concepts and terminology. In addition, training and education in pharmacogenetics for healthcare professionals is necessary if pharmacogenetics is to be successfully implemented and utilized (Dodson, 2011). Furthermore, an assessment of the educational needs of the patients, healthcare professionals, and clinics are necessary prior to any pharmacogenetics implementation.

### 1.1.3. VIEWS OF PATIENTS ON PHARMACOGENETICS

The majority of the U.S. population received their last formal science education in high school and further information regarding science education is pulled from outside resources (i.e. media, peers) (Trumbo 2000; Reilly, 2000). Therefore concept of health and the health care provided are rooted in outdated educational sources and may inhibit people from receiving optimal health outcomes for themselves. In order to understand

patients' reluctance to participate in pharmacogenetics research there should be discussions with patients to determine what necessary actions are needed to address their reluctance. Currently there is limited literature on patients' views on pharmacogenetics and pharmacogenetics testing; with a focus on how patients understand basic genetic concepts and genetic risks, which have suggested that patients are not very familiar with the concept of genetics and its links with medications (Fargher et al., 2007; Lanie et al., 2004; Emery et al., 1998). Therefore, opportunity exists to include a wider range of public participation since they are the target population in administering pharmacogenetic testing (Almarsdóttir et al., 2005). One U.S. study examined 62 adults (African Americans and Caucasians) who were asked questions related to basic genetic concepts (Lanie et al., 2004). There were some difficulties in defining the term "genetics", however about three quarters of respondents were able to give at least one defining characteristic by using a family example. When asked questions about the location of genes, 14% said genes were located in DNA or chromosomes, 24% mentioned genes in association with the brain and/or mind, and 34% of responses indicated that genes were in every cell. These data may illustrate that the public does have some grasp of genetics-related concepts, but also has shown how there still exists difficulty in differentiating these concepts. In the UK study (Fargher et al., 2007), 25 patients were interviewed on the topic of pharmacogenetics and pharmacogenetic testing. Three emerging themes were acknowledged: 1) familiarity with pharmacogenetics, 2) perceived beliefs of pharmacogenetic testing, and 3) characteristics of future pharmacogenetic tests. In theme 1, most of the patients' first impression of pharmacogenetics related to their knowledge of genetics and how we inherit certain things from our parents, while only half of patients

were able to define pharmacogenetics independently. In theme 2, patients noted perceived benefits, a few of which are personalized side-effect profile, reducing time to efficacious dose, and potential to predict most suitable therapies. Patients were noted as being enthusiastic about potential benefits, but also stressed how they expected pharmacogenetic tests to be delivered and explained with confidence by their healthcare provider. This finding in itself emphasizes the need of pharmacogenetic education for healthcare professionals in order for clinical uptake of pharmacogenetic testing services to occur. Lastly in theme 3, when patients were asked their opinion of how pharmacogenetic testing should be provided, it was clear that trust and familiarity were important in relation to healthcare provider and clinic. They had concerns with the turnaround time (~1-2 weeks) and how this could cause a potential delay in treatment. If the public are unable to understand concepts and terminology related to pharmacogenetics and pharmacogenetic testing, how are they to ask their doctors key questions or reap the potential benefits of this technology? This question is important to ask and address in terms of developing successful strategies that can educate the public. One way to do this with the public is by exploring the views and opinions of the patient community so they are better equipped to take advantage of all possible medical options to improve their outcomes.

## 1.2. COMMUNITY-BASED PARTICIPATORY RESEARCH

A majority of U.S. pharmacogenetics research has been conducted in European, African-American, Asian-American populations with limited data on AI/AN populations. The striking lack of data on genetic variation in U.S. AI/AN populations may be due in

large part to a legacy of mistrust toward U.S. institutions. Historically, U.S. institutions' role as definers and interpreters of community issues as well as "appropriators of human remains, cultural knowledge, and cultural artifacts" (Boyer et al., 2011) has generated mistrust among many AI/AN people. Furthermore, traditional research practices resulted in failure to return results in a culturally understandable format or conduct research beneficial for the community (Bowekey and Davis, 2003). In addition, two widely discussed examples of improper use of genetic research among indigenous people has made these communities appropriately wary of new research projects. In 1990, the Havasupai Tribe in Southwestern U.S. was experiencing a high prevalence of diabetes and agreed to give their blood samples to Arizona State University (ASU) researchers so they could understand this health issue. It was later discovered that the blood samples were subsequently used beyond diabetes to study mental illness, inbreeding, and Indian migration patterns. These very studies betrayed the trust and challenged the culture of the Havasupai Indians. In response, the Havasupai Tribe filed lawsuits against ASU and the researchers with the main legal claim being the violation of informed consent (Bommersbach, 2008). This case was settled with a monetary award to the Havasupai tribe members and also a return of their blood samples (Harmon, 2010). The other example involves the Nuu-Chah-Nulth people from British Columbia, Canada who agreed to participate in a genetic study in 1980 to address the high rates of rheumatoid arthritis in their community (Wiwchar, 2000). They donated over 800 blood samples to the University of British Columbia (UBC) to conduct this research study. However, UBC researchers were unable to find a genetic basis for arthritis in the tribal community, so blood sample were used to conduct studies regarding Indian migration patterns,

HIV/AIDS, and drug abuse research. These studies covered sensitive issues and exploited the Nuu-Chah-Nulth people. In 2004, a resolution between UBC and Nuu-Chah Nulth people was made to return blood samples back to the tribe. Furthermore, the tribe formed a Research Ethics Committee to review all future research studies to protect the tribe from harmful research (Wiwchar, 2004). These examples highlight the importance of transforming the way genetic research has historically been conducted with tribal communities.

Despite this negative history, researchers can still work with AI/AN populations and have moved towards the use of research models that recognize tribal sovereignty and self-determination (Davis and Reid, 1999). One such model, community-based participatory research (CBPR), is a qualitative research methodology in which the research institution and the community are fully partnered in every aspect of the research process, from determining research questions to analyzing, interpreting, and disseminating research findings. To this end, CBPR provides a framework to conduct collaborative research that builds upon trust, strength of both collaborators, and equality. CBPR has emerged as an ideal approach to identify and understand the priorities of a community and to address health inequalities that exist in these communities. Further advantages of research partnerships include enhanced practicality, quality, and validity to the research; engaging partners who can influence meaningful policy change; and building capacity among partners (Hoeft et al., 2013). Traditional models have consisted mainly of a paternalistic approach where researchers come in with all the questions and answers. The design of CBPR allows for researchers to work directly with communities to gain understanding and experience at the level of the community. In doing so,



communities are more equipped to engage in the research, gain knowledge, and come upon research results that are meaningful and reflect their priorities. From this perspective, a CBPR approach highlights the value of community action, cooperation, and responsibility amongst partners and therefore provides an appropriate framework in which to work with AI/AN communities (Boyer et al., 2007).

### 1.2.1 COMMUNITY-BASED PARTICIPATORY RESEARCH IN HEALTHCARE

Interest among academic research institutions in discovering new strategies to study and address complex health problems has increased with community demands for research that is conducted with communities rather than merely on communities. Specifically, research institutions are beginning to adopt research models that include expertise at the local level through the process of CBPR (George et al., 1996). The evidence of CBPR's emerging recognition is through support by the Institute of Medicine (IOM) in advocating that CBPR should be taught to all incoming healthcare professionals (Insitute of Medicine, 2002). The IOM described the utilization of CBPR in public health as "epidemiology enriched by contemporary social and behavioral science because it incorporates what we have learned about community processes and engagement, and the complex nature of interventions with epidemiology, in order to understand how the multiple determinants of health interact to influence health in a particular community" (Minkler and Wallerstein, 2008). Various new journals have been developed and devoted to CBPR (*i.e. Progress in Community Health Partnerships, Action Research, and CES4Health*) in the U.S. Furthermore, many divisions of the National Institutes of Health (NIH) have increasingly called for grant proposals requiring the use of a CBPR

framework to investigate and address health disparities and inequalities (Minkler and Wallerstein, 2008; Wallerstein and Duran, 2006). Success in addressing health inequalities in communities occurs when appropriate steps are taken to fully engage community partners to explore and take action in addressing the health issues of most concern in a community where they are deeply rooted.

### 1.2.2. COMMUNITY-BASED PARTICIPATORY RESEARCH WITH AI/AN COMMUNITIES

CBPR has been an effective model in conducting successful and scientifically sound research in AI/AN communities in the areas of substance abuse prevention (Mohatt et al., 2004; Ellis, 2003; Santiago-Rivera et al., 1998), environmental health (Severtson et al., 2002), breast cancer screening (Lantz et al., 2003), diabetes (Satterfield et al., 2003; Jernigan, 2010), and nutrition (Jernigan et al., 2012). These studies have published findings on health outcomes as well as development of culturally relevant CBPR methodology within their partner communities. Therefore, we chose to implement a CBPR approach in engaging AI/AN communities in pharmacogenetics research to help overcome issues of mistrust from previous research. In order for pharmacogenetic research to reach its optimal utility in AI/AN communities, a full understanding of genetic variation in these communities is necessary. To address the lack of AI/AN participation and inclusion in pharmacogenetics research, we have developed a partnership with the Confederated Salish and Kootenai Tribes (CSKT) living on the Flathead Indian Reservation in northwestern Montana. The CSKT community is comprised of three different tribes: Salish, Kootenai, and Pend d'Oreille. This academic-

community partnership is the first of its kind to focus on understanding pharmacogenetic variation in AI/AN populations in the U.S. The CSKT Tribal Council recently approved submission of a research publication that has emerged from this partnership (Fohner et al., 2013). Through the use of CBPR there is a potential to establish trust and reorganize power relationships such that community members become equal partners. CBPR involves the community at each stage of the research process, and must begin at the earliest stages if communities are to build capacity and ensure that the research reflects community priorities (Boyer et al., 2011). On-going consultation and qualitative research with CSKT partners will provide identification of barriers and interests in pharmacogenomics research and the use of pharmacogenetic tests in Tribal Health Clinics.

As the field of pharmacogenomics progresses, the involvement of AI/AN communities in pharmacogenomics research has the potential to bring forth culturally-relevant strategies in implementing pharmacogenetic tests in Tribal Healthcare and local facilities. Declining costs of pharmacogenetic tests and evidence for clinical utility will provide a strong and compelling case for introduction of pharmacogenetic testing in AI/AN communities. By building an infrastructure and a CBPR-based partnership, we learn more about therapeutic problems and priorities within our partner communities.

### 1.3. SPECIFIC AIMS

The goal of these studies was to test the hypothesis that CBPR methods provide a strong basis for addressing knowledge gaps related to pharmacogenetics in AI/AN communities. To accomplish this goal, several CBPR approaches were used and are

described in three specific aims. The goals of Aim 1 were to build capacity in the areas of pharmacogenetics research in the CSKT and to work with members of the Community Pharmacogenetics Advisory Council (CPAC), the oversight committee for the project, to develop culturally appropriate materials for use in qualitative research. In Aim 2, we conducted healthcare provider interviews with Montana providers who serve CSKT peoples to explore the acceptability and feasibility of implementing pharmacogenetic testing into Tribal Health. Finally in Aim 3, we conducted focus groups with enrolled CSKT members to explore their interest in participating in pharmacogenetics research, views of pharmacogenetic testing, and ideas of dissemination. These CBPR methodologies included community education in the form of genetics-related and CBPR-related workshops. The following chapters outline the steps completed thus far to achieve the aforementioned aims of the thesis.

**Table 1.1. List of Clinically Relevant Pharmacogenetics Examples**

<b>Gene</b>	<b>Drug</b>
<i>DPYD-5FU</i>	Capecitabine
<i>CYP2C9</i>	Warfarin Phenytoin Tolbutamide
<i>CYP2C19</i>	Clopidogrel Diazepam
<i>CYP2D6</i>	Codeine Tamoxifen SSRIs Tricyclic antidepressants
<i>TPMT</i>	Azathioprine Mercaptopurine Thioguanine
<i>UGT1A1</i>	Irinotecan Nilotinib
<i>OATP1B1</i>	Simvastatin
<i>HLA-B</i>	Abacavir Allopurinol Carbamazepine
<i>VKORC1</i>	Warfarin

*Table adapted and compiled from the Clinical Pharmacogenetics Implementation Consortium guidelines and [www.pharmgkb.org](http://www.pharmgkb.org)*

**Table 1.2. Product Labeling: Available Pharmacogenetic Tests**

<b>Genetic Biomarkers</b>	<b>Clinical Context</b>
<i>CYP2C9/VKORC1</i>	CYP2C9 and VKORC1 testing is recommended to optimize dosing regimen for warfarin.
<i>CYP2D6</i>	CYP2D6 testing is recommended for high-risk populations to prevent toxicities in treatment with codeine and to improve therapeutic efficacy for breast cancer patients in treatment with tamoxifen.
<i>HLA-B*1502</i>	HLA-B testing is recommended before initiating treatment with carbamazepine (Tegretol, Equetro)
<i>HLA-B*5701</i>	HLA-B testing is recommended for high-risk populations before initiating treatment with abacavir (Ziagen)
<i>TPMT</i>	TPMT testing is recommended before starting treatment with azathioprine (Imuran)

*Table adapted and compiled from U.S. FDA Table of Pharmacogenomic Biomarkers in Drug Labels and <http://www.pharmkgb.org>*

## CHAPTER 2

### COMMUNITY-BASED PARTICIPATORY RESEARCH TO FACILITATE COMMUNITY INVOLVEMENT AND ENGAGEMENT WITH CONFEDERATED SALISH AND KOOTENAI TRIBAL MEMBERS

*This chapter is being prepared for publication*

## 2.1. INTRODUCTION

Over the past decade, substantial advances in genetic research have enhanced understanding of genetics as an important contributor to individual variation in medication response, leading to the area of research called pharmacogenetics (Evans and Relling, 1999; Lesko and Schmidt, 2012). The translation of pharmacogenetics research into genetic tests has the potential to help clinicians identify patients at risk of treatment failure due to excessive toxicity or lack of efficacy (Crews et al., 2012; Roth et al., 2011). Genetic research typically does not directly answer health questions that are priorities for a community. Pharmacogenetic research, however, is one type of genetic research that could have clinical applications that are of particular benefit to a community should the results lead to ways in which health providers can improve drug response and avoid adverse drug reactions. Thus, pharmacogenetic research may fit better within a community-based participatory research (CBPR) approach to identify health priorities of the community and also lends itself to power-sharing or bidirectional learning and teaching. While there is much evidence that pharmacogenetic variation is diverse across ethnic groups, American Indian and Alaska Native (AI/AN) people have largely not been included in pharmacogenetic studies, thus limiting the possibility for implementation of pharmacogenetic testing. To address this lack of AI/AN populations in pharmacogenetics research, we have developed an academic-community partnership with the Confederated Salish and Kootenai Tribes (CSKT) living on the Flathead Reservation in northwestern Montana.

A premise of this work is that pharmacogenetic testing should be accessible to all members of society, but that lack of evidence from AI/AN populations may limit the



benefits of pharmacogenetics for these groups. Research involving AI/AN populations is needed, but there is a legacy of mistrust among AI/AN communities towards academic research, particularly towards genetic research, and a perception that past health research has provided little benefit (Tsosie, 2007; Reardon and TallBear, 2012). Furthermore, conventional research practices often fail to address community priorities or to return results to the community in an understandable, culturally relevant form (Bowe Katy and Davis, 2003; Boyer et al., 2011). In addition, two high-profile examples of inappropriate genetic studies in AI/AN communities have made AI/AN communities wary of genetic research. The first example was a rheumatoid arthritis study in the Nuu-Chah-Nulth First Nation in British Columbia, Canada, where University of British Columbia researchers conducted additional studies on HIV/AIDs, drug-abuse, and human migration without the permission of the tribe (Wiwchar, 2000). The second example involved a diabetes study in the Havasupai Tribe in Southwestern United States. Arizona State University (ASU) researchers partnered with the Havasupai to conduct a genetics study to address questions pertaining to diabetes; however, researchers used donated Havasupai blood samples for additional studies on inbreeding, schizophrenia, and historical migration (Harmon, 2010). In both instances, researchers went beyond their agreements with the communities to share samples with other investigators and conduct research outside the scope of community approval. Fortunately, in the Havasupai case, the National Congress of American Indians passed a resolution to support the Havasupai Indian Tribes in their lawsuit against ASU; claiming that ASU researchers misused tribal blood samples (National Congress of American Indians, 2006). These examples have resulted in adverse

impacts on indigenous communities and highlight the importance of transforming the way genetic research is conducted within tribal communities. .

A key strategy in addressing the mistrust of researchers and transforming research practice has been implementation of CBPR to identify and understand the priorities of a community and to address health disparities that exist in these communities. CBPR refers to collaborative research where communities are treated as equal partners and are involved in all stages of the research project to ensure that community needs are prioritized (Boyer et al., 2011; Christopher et al., 2011). Furthermore, AI/AN communities advocate for a CBPR model when conducting research because it facilitates their participation in and overseeing of the research process; thereby reducing the risk of abuse and helping to build trust (Burhansstipanov et al., 2005). We established a partnership between the University of Montana (UM), the University of Washington (UW), the Montana Cancer Institute Foundation (MCIF), and the CSKT Tribal Health and Human Services based on CBPR principles in order to conduct pharmacogenetic research. This effort is part of a center that has partnered with AI/AN communities in Alaska, Montana, and Washington called the Northwest–Alaska Pharmacogenomics Research Network (NWA-PGRN) to study pharmacogenetics in rural and underserved AI/AN populations. The NWA-PGRN is part of a national network, the Pharmacogenomics Research Network (NWA-PGRN), funded by the National Institutes of Health to use genetic information to improve response to medications. We have recently published one of the first studies in the United States about pharmacogenetic variation in an AI/AN population (Fohner et al., 2013). This study was made possible through the partnership we have initiated in the CSKT community where the community

identified response to cancer medications as one of their health priorities. This partnership provides opportunities for the community to learn about research, specifically pharmacogenetics, and also provides guidance to the researchers about cultural appropriateness and cultural beliefs. .

## 2.2. MATERIALS AND METHODS

### 2.2.1. ESTABLISHMENT OF RESEARCH PARTNERSHIPS

The partnership between researchers at UM and MCIF and personnel at CSKT Tribal Health and Human Services began with initial meetings in 2007 to discuss how pharmacogenetics research might be conducted on the Flathead Reservation to evaluate the potential benefits of this type of research. These meetings were between researchers from the Department of Biomedical and Pharmaceutical Sciences at UM, an oncologist and clinical coordinator at MCIF, and the Department Head and Medical Director from Tribal Health. We made presentations to the CSKT Tribal Council to ensure community priorities were being met and to gain community approval of the research focus. The NWA-PGRN employs a total of 3 tribal members between the UM and CSKT Tribal Health research team which has played a fundamental role in appropriately navigating through tribal approval systems and further guiding the research project to reflect CSKT community needs.

As the partnership progressed and we started to seek research funding, discussions were initiated between the groups in Montana (UM, MCIF, and CSKT Tribal Health), researchers at the UW, and other research partners in Washington and Alaska to submit a

grant to the NIH PGRN to form the NWA-PGRN center. We sought approval from CSKT Tribal Council in May 2009 to apply for the grant and Council provided a letter of support for the submission. Funding for the NWA-PGRN started in July 2010. CSKT Tribal Health received a subcontract from the NWA-PGRN grant that includes support of a portion of the salary of the collaborating physician and blood-drawing supplies. In addition to Tribal Council approval, approval was obtained from the Institutional Review Boards of UM and UW.

#### 2.2.2. FORMATION OF COMMUNITY PHARMACOGENETICS ADVISORY COUNCIL

One of the major goals of the NWA-PGRN in Montana was to establish a community oversight committee, the Community Pharmacogenetics Advisory Council (CPAC), to assure Tribal input into the research project and strengthen the academic-community partnership. The Department Head and Medical Director of CSKT Tribal Health provided suggestions of people whom they thought would be valuable to have on the CPAC; they suggested representatives from both the Salish and the Kootenai Cultural Committees, staff at Tribal Health and Tribal Council, cancer survivors, and a student at Salish Kootenai College would provide a wide perspective from across the community. Tribal Health initially sent invitations out to six people to join the CPAC and all of them accepted; the first CPAC meeting was held November 2010. Since that first meeting, however, three people have had to leave the group because of other time commitments, and an additional four people were invited to join. Currently, seven people are members of the CPAC.

We hold monthly meetings with the CPAC to review study progress and goals on an ongoing basis. CPAC meetings provide a forum to discuss Tribal interest in pharmacogenetic research, culturally appropriate research practices, and the potential for the use of pharmacogenetic testing in Tribal healthcare settings. The CPAC has helped in the development of tools for focus groups that will be discussed later. Additionally, members of the CPAC accompanied UM researchers and Tribal Health staff when we presented to Tribal Council in February 2013 in order to get approval to submit a manuscript of the pharmacogenetic variation observed in CSKT people (Fohner et al., 2013).

### 2.2.3. CAPACITY BUILDING AND COMMUNITY ENGAGEMENT

We have engaged in a number of community engagement and capacity building activities geared toward increasing community knowledge and involvement in the pharmacogenetics project (See Table 1). One of the major goals was to educate CPAC members about pharmacogenetics research so that they can be better equipped to advise the researchers and educate other Tribal members. We have held two workshops for CPAC members: Genetics Education for Native Americans (GENA®) (Native American Cancer Initiatives, Pine, CO) and nDigiDreams Digital Storytelling (Santa Fe, NM). CPAC members were asked to fill out a survey to learn whether they found the workshops valuable and if the workshops were usefulness as an educational tool. Furthermore, using Likert-scale questions, the survey assessed the degree of knowledge CPAC members felt they had in the area of pharmacogenetics and whether participation in the CPAC has improved their knowledge.

The GENA® workshop provided a science curriculum tailored to an AI/AN audience to increase training in the area of genetics. The workshop consisted of educational presentations on the basics of cell biology and genetics, pharmacogenetics, and CBPR; and interactive exercises to increase learning and understanding. There were also designated discussions about ethical issues in research and ways to talk about genetic research within the CSKT community. The overall goal of GENA® is to assist AI/ANs with informed decision-making regarding participation in genetic research projects. GENA® workshops have been used in AI/AN communities for over a decade and have been very successful in educating participants in a culturally tailored manner (Dignan, et al., 2005). A 2-day GENA® workshop was held for CPAC members, Tribal Health staff, CSKT community members, and researchers from MCIF, UM, and UW in May 2011. Educational objectives from the GENA® workshop are presented in Table 2.

#### nDigidreams Digital Storytelling Workshop

Storytelling has been one of the dominant ways of societal communication since ancient times. Among AI/ANs, storytelling has been used to share history, heritage, and customs in order to keep their legacies alive (Hodge et al., 2002). We held a workshop that takes a modern approach to traditional storytelling called digital storytelling. Digital storytelling involves telling a personal story using video, music, and voiceover. The workshop was conducted by nDigiDreams (Manuelito and Rodriguez, 2013) an indigenous-focused consulting company that trains individuals to use media tools for the purpose of creating digital stories focused on health and wellness. A 3-day nDigidreams workshop was held in February 2012 with CPAC members, CSKT community members,

and researchers from MCIF and UM. This digital story training involved writing and recording a narrative, producing a storyboard with images and music, and final assembly of a video.

#### 2.2.4. DEVELOPMENT OF FOCUS GROUP MATERIALS

Little is known about how AI/AN people view participation in pharmacogenetic research. To understand the views of CSKT people about pharmacogenetic research and the potential for application in healthcare, UM and UW researchers and the CPAC worked together to create a moderator's guide for community focus group discussions. CPAC members gave input on successive versions of the moderator's guide and participated in "mock" focus group themselves as part of the planning process only. CPAC members also gave suggestions on the organization of the focus group to promote conversation. and recruitment of focus groups, with the CPAC members also agreed to help in recruitment for focus groups by inviting people they knew in the community, distributing flyers, and placing advertisements in the local *Char-Koosta News* (Azure, 2013b). To help in recruitment, CPAC members were given informational packets that included information about the pharmacogenetics research project, contact information for all researchers, and specific information about what participation in a focus group would entail.

### 2.3. RESULTS

#### 2.3.1. COMMUNITY PHARMACOGENETICS ADVISORY COUNCIL

We established the CPAC to increase Tribal input into the pharmacogenetics research project. To support the CPAC in giving feedback to the research team and

explaining the NWA-PGRN project to community members, we offered educational opportunities to help CPAC members become more comfortable with genetic concepts and terminology. To gauge whether these educational programs were useful and effective at community pharmacogenetics, we administered a survey at a regular CPAC meeting that ask CPAC members to rate their knowledge of pharmacogenetics prior to and after joining the CPAC. The Likert scales were designed on a scale of 1 to 5, with 1 reflecting “considerable knowledge” of pharmacogenetics and 5 reflecting “no knowledge” of pharmacogenetics . The average score of CPAC members knowledge prior to joining the CPAC was 4.5 (median: 5), suggesting they had little to no knowledge of pharmacogenetics research. The average score after joining the CPAC was 2.75 (median: 3), suggesting that CPAC members felt their knowledge of pharmacogenetics had improved. Not only did the average score improve, but every individual member of the CPAC reported an increase in knowledge prior to and after joining CPAC.

Furthermore, CPAC members’ views about pharmacogenetics research may have shifted. Prior to joining the CPAC, members voiced two major themes in the survey: either they had not heard of this type of research or they had heard of it but were “Skeptical. Worried that the Indian people might not benefit from the research” Another member mentioned, “Actually I never did hear of pharmacogenetics, let alone spell it.” After joining the CPAC, comments suggest that CPAC members are more supportive of pharmacogenetics research. One member who had previously stated feeling “suspicious” of pharmacogenetics now reported: “After seeing the potential for medical breakthroughs in helping tribes, I am more inclined to support guided research, especially in the area of



informing and educating the population.” Another member reported how they now have a “More positive outlook with the potential outcomes for the people (reservation and tribal people).” The feedback the researchers have heard from the CPAC through this survey and during meetings is that consistent discussions with the CPAC has been useful in educating our partner community in the area of pharmacogenetics research, but that continued education in genetics and pharmacogenetics is important.

### 2.3.2. GENETIC EDUCATION FOR NATIVE AMERICANS WORKSHOP

We had two goals for the GENA® workshop: to increase pharmacogenetic knowledge within our partner community members and to increase cultural awareness and sensitivity within our research team. In previous work, GENA® has reported a 35% increase in participants’ knowledge, based on pre- and post-workshop surveys administered. In the survey that was conducted with the CPAC, we asked questions to assess the value of the GENA® workshop and all members agreed that it was helpful in expanding their knowledge in the area of genetics and pharmacogenetics. For example, one member stated, “I got a good idea about genetics and DNA and Indian people. It has spurred me to explore the subject more.” This feedback supports the importance of providing education to our partner CSKT members.

### 2.3.3 NDIGIDREAMS DIGITAL STORYTELLING WORKSHOP

Researchers and CPAC members each produced a 3-5 minute personal narrative digital story, and learned the skills to facilitate creation of additional digital stories in the community. We have used these digital stories to raise awareness about pharmacogenetic

research with the CSKT people and to increase participation in the project during recruitment events (e.g. pow-wows, health and career fairs). We also asked CPAC members to evaluate this workshop in the survey. Three CPAC members had attended the GENA workshop and all felt that the workshop was helpful in developing skills for creating digital stories and that it would be a useful method for communicating pharmacogenetics research. Therefore, in the future we plan to use these digital stories, as well as to generate additional stories, and show them on local access TV stations, websites, and in CSKT Tribal Health clinics.

#### 2.3.4 FOCUS GROUP MATERIALS

Together with the CPAC, we have created a culturally appropriate moderator's guide for focus groups to discuss views of pharmacogenetics. Their involvement ensured the moderator's guide reflected the values and approaches that the CSKT community would find understandable and culturally appropriate. The "mock" focus group was attended by four of our CPAC members and helped to further elicit feedback for the moderator's guide and focus group organization. For example, CPAC members mentioned how in their culture elders are respected by the youth and in a social setting it is seen as disrespectful for youth to speak up first in front of an elder. Therefore, CPAC members recommended we stratify focus group participants by age (<40 years of age and ≥40 years of age) so that the youth and elders are grouped separately, which might encourage more dialog from all participants in the focus group. The "mock" focus group also prompted CPAC members to provide more informed feedback on the moderator's guide regarding the types of questions asked, the order in which they were asked, and the

appropriateness of the language for a generally lay audience with minimal or no genetic science background. The questions in the guide revolve around three major themes: 1) the field of pharmacogenetics, 2) clinical utility of pharmacogenetic tests 3), dissemination of results back to community (See Table 3 for specific examples). We also discussed with the CPAC whether to stratify participants in the focus groups, and decided we will stratify by age Researchers from the UM, accompanied by some CPAC members, presented before CSKT Tribal Council and received approval to start recruitment for focus groups in February 2013. The goal of these focus groups is to facilitate tribal input regarding cultural barriers and understanding in pharmacogenetics research and its translation into the clinic.

## 2.4 DISCUSSION

We have established an academic-community partnership between CSKT providers and community members and researchers at the UM, UW, and MCIF to explore the potential benefits of pharmacogenetic testing in CSKT Tribal Health and Human Services, the healthcare entity through which the majority of CSKT members receive their healthcare. We have used CBPR approaches, particularly in the formation of the CPAC advisory group, to engage academic and community partners to develop bidirectional expertise and ensure that the community is an equal partner in the research project. We have sought authorization in all aspects of the research project from the CSKT Tribal Council, Tribal Health, and members of the CPAC before initiating any project activities.

AI/AN communities have been wary of participation in genetic research because of a negative history of researchers and a mistrust of United States academic institutions

and the Federal government. CBPR has shown to be a promising research approach by providing a framework from which to conduct research within AI/AN communities and establishing a mindful path in creating a trusting and equal partnership with the CSKT community (Burhansstipanov et al., 2005; Boyer et al., 2011; Thomas et al., 2009). We have learned that achieving successful implementation of the CBPR approach requires forthright understanding and acknowledgement of AI/AN communities as a sovereign cultural people. Only the communities themselves fully understand their cultural structure and beliefs, and there is knowledge to be gained for researchers to work productively with these communities.

One of the key features of our CBPR approach was the establishment of the CPAC, which has brought invaluable community insight to help guide the research in a culturally sensitive direction. Regular meetings between the researchers and CPAC increase Tribal input into the research study, give advice about the study approaches to ensure cultural appropriateness, and discuss Tribal interest in pharmacogenetic research and the use of pharmacogenetic testing in health care. After being involved with the CPAC, a member stated that they had a “more positive outlook with the potential outcomes for the people (reservation and tribal people).” Since the establishment of the CPAC, we have seen an increase in pharmacogenetics knowledge and a shift in negative perceptions and attitudes towards this type of research. Educational workshops with the CPAC and other community members have helped increase community involvement and engagement and provided CPAC members with more tools to make informed discussions and recommendations about the research project. The CPAC has also been crucial in the development of informational materials that describe the pharmacogenetics research

project. Another way in which a CPAC member, Bernie Azure, has also increased community awareness and education about the research project through several articles he wrote and published in the *Char-Koosta News* (the CSKT newspaper) (Azure, 2011; Azure, 2012a; Azure, 2013c; Azure, 2012b).

The next step for the research project will be to conduct qualitative research in the form of focus groups to assess views about pharmacogenetics research in the CSKT community. Recruitment strategies have already been discussed and initiated with the CPAC. The CPAC members have collectively handed out educational brochures and recruitment flyers throughout the Flathead Indian Reservation (i.e. Tribal Health clinics, Salish Kootenai College). The CPAC assisted in creating focus groups materials, particularly the moderator's guide. Their involvement ensured the moderator's guide reflected the values and approaches that the CSKT community would find understandable and culturally appropriate.

An important aspect of this partnership is that the researchers frequently present before the CSKT Tribal Council to provide updates about research progress, to gain approval for submission of manuscripts, and to ask for approval for new research directions. After we published the first academic paper to come out of this partnership after receiving Tribal Council and Tribal Health approval (Fohner et al., 2013), we worked with the CPAC to deliver the results in formats that would be more understandable. CPAC member, Bernie Azure, wrote one article in the *Char-Koosta* newspaper discussing the primary results (Azure, 2013a). We also have discussed using our training from the nDigidreams digital storytelling workshop to create new stories that could be useful in disseminating research findings in the community.

Despite the many benefits to the CBPR approach, associated challenges did arise. For instance, current educational efforts have only begun to reach our CPAC and a small portion of the CSKT community. In the case of the workshops we conducted, only a small number of CSKT community members were able to participate due to limited funding resources. However, as we continue to bring awareness and engage more of the community, we hope to involve a larger portion of the CSKT community. Another challenge involves CSKT community approval, where long approval times are needed in order to obtain consent from Tribal Health, Tribal Council, and the Salish and Kootenai Cultural Committees for research project activities and publication. Thus, coordination of the tribal review process with the university reviews process proved difficult. Although this grant has accounted for time in developing a partnership and flexibility for the CSKT community to provide input in the research project focus and goals; so as a result postponement of deadlines was occasionally necessary. However, these challenges are an important reminder that the partnership with the CSKT community is process oriented and therefore success lies in the ability to be patient and work at the pace set by the community.

The goal of this academic-community partnership has been to work collaboratively to ensure that the CSKT community has sufficient knowledge about pharmacogenetics research and to gain their input to develop culturally appropriate strategies for the project. Results generated from the research project have the potential to address major unmet medical needs. A key strategy in engaging the CSKT in pharmacogenetic research was the implementation of CBPR to identify the priorities of the community and to build mutually productive partnerships to address health

disparities. AI/AN populations have for the most part been left out of pharmacogenetic research, and thus have been overlooked in the advancement of personalized medicine. The use of a CBPR approach to involve AI/AN communities in pharmacogenetics research has the potential to implement pharmacogenetic tests in Tribal Healthcare and local facilities to improve therapeutic efficacy and safety.

**Table 2.1. Capacity Building and Community Involvement Action Activities**

<b>Components</b>	<b>Activities</b>
Community Education	Community Pharmacogenetics Advisory Council Materials development and review Media (i.e. Char-Koosta News) GENA® workshop
Community Training	nDigiDreams workshop Recruitment materials development and review
Partnership Advocacy	Facilitate connections among researchers, healthcare providers, and CSKT community Establish sustained funding for CBPR continuation



**Table 2.2. Educational Objectives from the GENA® Workshop**

<b>Objectives</b>	<b>Descriptions</b>
Objective 1	What is a cell? Describe parts of a cell*
Objective 2	Review basic principles of cell biology and genetics; e.g., cell structure, location of DNA and RNA, protein expression, transcription, and translation
Objective 3	Review basic genetic concepts*
Objective 4	Understand classical patterns of inheritance and cultural traditions related to these patterns*
Objective 5	Community-based participatory research case studies
Objective 6	Describe benefits and drawbacks to pharmacogenetic
Objective 7	Ethical issues case studies
Objective 8	Ethics, Opinions
Objective 9	Questions and discussion about ways to talk about genetics in the CSKT

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\* Objectives also include an interactive participant exercise

<http://www.natamcancerinitiatives.org/GENA/GENA.html>

(Dignan, Burhansstipanov, and Bemis 2005)

**Table 2.3 Examples of Moderator’s Guide Questions for Focus Groups**

<b>Themes</b>	<b>Examples of Questions</b>
Field of pharmacogenetics	<ul style="list-style-type: none"><li>• What do you think about genetic research aimed at understanding how medications work?</li><li>• What do you think about Salish and Kootenai people participating in genetic research?</li><li>• What are some things we should be thinking about culturally when doing this kind of pharmacogenetic research in Tribal populations?</li></ul>
Clinical utility of pharmacogenetic tests	<ul style="list-style-type: none"><li>• What do you think about a genetic test that would help the doctor figure out the right dose of warfarin for a person who was at risk of developing a dangerous clot?</li><li>• What do you think about a genetic test that would help the doctor figure out whether tamoxifen is the best medication for a person being treated for breast cancer?</li></ul>
Dissemination of results back to the community	<ul style="list-style-type: none"><li>• What kind of information would you want researchers to share with your community?</li><li>• What would be the best way for researchers to share information with the community and in what format would be best?</li></ul>

## CHAPTER 3

# HEALTHCARE PROVIDERS' VIEWS ON PHARMACOGENETICS RESEARCH AND ITS FUTURE IMPLEMENTATION INTO THE CONFEDERATED SALISH AND KOOTENAI TRIBAL HEALTH CLINICS

### 3.1. INTRODUCTION

Pharmacogenetics encompasses the study of genetic variation and how this relates to an individual's drug response. Pharmacogenetics research has been aimed at discovering these sources of genetic variation to guide therapy in patient treatment (Vesell, 2000; Cordell and Clayton, 2005). One way that this is being done is through the use of pharmacogenetic testing. Pharmacogenetic tests provide the ability to identify patients at risk of adverse drug reactions before treatment is initiated. In several therapeutic areas (i.e. oncology, cardiology, psychiatry), there are various pharmacogenetic tests that have been adopted and applied for patient care (Ventola, 2011). For example, the antiretroviral drug, abacavir, is primarily used to treat people with human immunodeficiency virus and evidence has shown that ~6% of patients experience life-threatening hyper-sensitivity reactions; therefore, healthcare providers are recommended to test for clinically significant HLA variants in this patient population (Martin et al., 2012). This example shows how a test can help avoid an adverse drug reaction and the use of such tests are being encouraged by regulatory agencies, such as the FDA.

However, implementation of pharmacogenetic tests into the mainstream medical community has been slow and challenging. Some reasons for this is that there is little clinical evidence that evaluate the utility of pharmacogenetic tests, the medical community is unaware of pharmacogenetic testing, or there is no clear model of how to implement pharmacogenetic testing into the healthcare system (Roth et al., 2011; Rogowski et al., 2009; Grossman, 2007). In order to successfully integrate pharmacogenetic testing into the healthcare clinics, consultation with the medical

community in which you plan to implement is crucial. Healthcare providers facilitate medical treatment, understand the socioeconomics of their healthcare sites and patient community. Therefore discussions with healthcare providers will provide valuable insight to the feasibility of pharmacogenetic testing in their healthcare facilities.

There is limited published data about the views of healthcare providers regarding pharmacogenetics research and its translation into the clinics. One study that was published, explored U.S. healthcare provider views on the risks and benefits of pharmacogenetics research using qualitative methods consisting of a three day workshop where discussions around this topic were facilitated (Formea et al., 2013). Another U.S. study evaluated healthcare provider views on the adoption of pharmacogenetic testing in clinical practice by administering of a national survey (~10,000 respondents) (Stanek et al., 2012). A U.K. study held interviews and focus groups with healthcare providers to explore their views about pharmacogenetics research and its translation into the clinic (Fargher et al., 2007). Therefore, it is of value to include a wider range of healthcare provider views on the topic of pharmacogenetics and its translation into the broader medical community. This study used consultative and qualitative methods to evaluate the views of healthcare providers on the potential benefits and harms of pharmacogenetic testing, its acceptability in rural and tribal communities, and the feasibility of implementing pharmacogenetic testing into clinical practice.

### 3.2. METHODS

### 3.2.1. STUDY SUBJECTS

Healthcare providers involved in the study were identified by research team members at the University of Montana, CSKT Tribal Health, and the Montana Cancer Institute Foundation. Seventeen interviews were conducted: 10 physicians, 3 registered nurses, 2 nurse practitioners, 1 physician's assistant, and 1 pharmacist. There were a total of 10 females and 7 males with ages ranging from 30-65yrs. Healthcare providers represented Missoula clinics (9 total) and Polson clinics (8 total), of these providers 7 were associated with Tribal Health. Also, 3 healthcare providers were tribally affiliated. All of the healthcare professionals treated AI/AN patients.

### 3.2.2. HEALTHCARE PROVIDER INTERVIEWS

The interviews were conducted to facilitate conversations with healthcare providers to try to understand potential benefits and harms of genetic testing and to learn about how a patient's likely drug response might be used in clinical practice. Individual healthcare providers were engaged in a series of discussions using structured deliberative processes and the interviews consisted of three main sections: 1) attitudes regarding pharmacogenetic testing, 2) card sort exercise – assigning values to different kinds of pharmacogenetic tests that exemplified drug efficacy (selective serotonin reuptake inhibitors, SSRIs), drug dose and monitoring (warfarin), and adverse drug events (carbamazepine), and 3) clinical integration. Face-to-face interviews were held at healthcare provider's place of work and lasted approximately one hour. All subjects consented to the study using forms approved by the University of Montana Institutional Review Board.

### 3.2.3 Qualitative Analysis

Trained members of the study team at the University of Washington constructed an initial coding template drawing from the interview guide and themes that arose from the individual interview sessions. This coding template was reviewed by the collaborative research team at University of Montana and University of Washington who had expertise in qualitative research to achieve consensus. The interviews have been transcribed verbatim and are in the initial stages of coding using thematic analysis. Initial coding was performed using the Dedoose© qualitative analytical software package (Los Angeles, CA) and the revised coding template.

## 3.3 RESULTS

### 3.3.1 HEALTHCARE PROVIDER INTERVIEW ANALYSIS

The goal of these deliberative processes was to facilitate discussion about the potential benefits and harms of pharmacogenetic research and whether its translation into CSKT facilities is feasible. Nineteen major themes were captured throughout the analysis process that encompassed the views and opinions of all 17 healthcare providers. These themes are as follows:

1. *Genetics and genomics-general*: Comments related to the ability of healthcare providers to differentiate between genomics and pharmacogenomics. Comments categorized under this code may also include genetics-related concerns and general pharmacogenomics perceptions. Respondents were asked questions about

the idea of introducing a whole genome screening test that would be accessible for medical purposes. One respondent acknowledged that:

*“...there’s so many issues there. I mean there’s medical issues, there’s ethical issues. You know, there are, there could be a lot of psychological issues that arise if somebody’s fearful there whole life they’re gonna get the same disease that, you know, Auntie May got.” (Respondent 670)*

This respondent went on to explain that applying a more targeted approach to genetic screening instead of a shotgun approach may elicit a more positive response with the medical and patient community. General thoughts on genomics and pharmacogenomics by healthcare providers included the push for efforts in advancing technology that will incorporate pharmacogenetic testing results.

2. *Genomics and pharmacogenomics differentiation:* Comments related to the ability of healthcare providers to differentiate between genomics and pharmacogenomics. Comments categorized under this theme may also include genetics-related concerns and general pharmacogenomics perceptions. Most healthcare providers were able to differentiate between the concept of genomics and pharmacogenomics. Respondents emphasized the point that pharmacogenomics is more personal than the basic lab tests (i.e. blood sugar, blood type). One respondent explained this personal difference as:

*“I think it has a lot to do with the word genetics in the name [referring to test]. Because we do PT/INR, we monitor warfarin or heparin, whatever we got going.*



*Yeah I think that the word genetic...I think cuz it goes to us personally, it's like finding out our secrets. Maybe we're not genetically perfect." (Respondent 765)*

Other respondents further described pharmacogenetic testing as eliciting more information such as having a *breast cancer 1* mutation that encodes damaging effects of the breast cancer 1 protein, which is important for DNA repair; and therefore, increases the likelihood of developing cancer. However, healthcare providers still felt that it would be worthwhile to investigate drug response at the individual level.

3. *Implementation – policy and operations*: Comments related to policies, procedures, and trainings that would be required in implementing a pharmacogenetic test. Healthcare providers' general response to policies and procedures were that pharmacogenetic tests should be equal to other established tests in the clinic in their physical use (i.e. ordering process, availability in house). Furthermore, most healthcare facilities contain electronic medical records: therefore, respondents were more likely to use pharmacogenetic information to treat their patients if test results were incorporated into electronic medical records in the form of prompts. It was also emphasized that upon implementation of pharmacogenetic testing, a policy and procedure manual should be written specifically for pharmacogenetic testing guidelines and be made available in clinics. Some respondents mentioned available trainings that occur at their healthcare sites that did not include much on the topic of pharmacogenetics. Most healthcare providers received information on pharmacogenetics through trusted

resources such as the National Comprehensive Cancer Network (a source of cancer information and treatment guidelines compiled from multiple leading cancer centers), Up-To-Date (an evidence-based resource for clinical information compiled by physicians), and peer-reviewed journals. For the latter, one respondent mentioned how peer-reviewed journals are important in contributing to policy and procedures of pharmacogenetic testings:

*“The most convincing thing is publication in a peer-reviewed journal that is then able to be put to the scrutiny of the peers, and after being assessed with that scrutiny still seems to be valid. Then those are the things that move into clinical care.” (Respondent 582)*

These results show the various avenues of pharmacogenetics education and awareness relied on by healthcare providers as well as their opinions in how policy and procedures should look for pharmacogenetic testing. A lack of training seems to be common across healthcare sites, most likely due to pharmacogenetics testing still being in the research stage.

4. *Implementation – success factors*: Comments related to factors that will be important for the implementation of a pharmacogenetic test. Respondents were insistent that electronic medical records be utilized in efforts to implement pharmacogenetic information and test results in an understandable format. This would provide a user-friendly appeal to healthcare professionals and increase their support and use of pharmacogenetic tests. Another concern that was mentioned

involved researchers' need to explore bioethical questions within tribal communities. One respondent explained:

*"...I think it's important to be aware of the historical trauma, mistrust, and also being, coming in and talking to the leaders in our community [CSKT community] and in a respectful way, not talking above, but talking in layman's terms to try to best explain what they see as the benefits of bringing this kind of testing to our people [CSKT people]." (Respondent 775)*

Furthermore, healthcare providers suggested that evaluating pharmacogenetic testing in clinics and proving its usefulness will help to increase its use in healthcare institutions.

5. *Pharmacogenomics barriers*: Comments about factors that could limit the uptake of available pharmacogenetic tests. The common barriers that seemed to surface across all interviews on the side of healthcare providers and clinics is the issue of cost to implement a genetic test and older generations not believing in the benefits of pharmacogenomics.

*"Cost is the big thing and geographical location. I mean in Montana, getting people...I worked briefly here after I moved back and unfortunately the hospital I worked at did not see any benefits to tumor typing and genetic testing before doing the chemotherapy...And rather than working as a collaborative for the patient's benefit, we have some people who are very resistant." (Respondent 100)*

In terms of patients, ethical issues regarding abuse (i.e. exploitation, stigmatization) of their genetic information, mistrust, and reluctance out of want

for privacy or other personal reasons were the main barriers that arose from the interviews.

*“...Just any genetic sequencing, you know, has potential ethical grey zones, that’s always the argument that seems to come up is, what about abuse? A cheek swab doesn’t just give you information about drug metabolism, it gives you your entire code.”*

*(Respondent 865)*

Barriers are important to evaluate and discover in order to successfully implement pharmacogenetic testing, our studies have identified various barriers that will guide our research in overcoming them.

6. *Pharmacogenomic benefits*: Comments related to the value of pharmacogenomic tests in clinical practice, or how they could offer value in the future. Benefits could refer to either specific medications or to more general benefits. Healthcare providers talked about the potential benefits in guiding drug therapy, predicting adverse side effects (i.e. toxicity), increasing survival rates, and saving time, resources, and energy. Healthcare providers further explained how these benefits apply to narrow therapeutic range drugs and a focus should be on drugs targeting diabetes, cardiovascular disease, and cancer. One provider explains how pharmacogenetics can prove useful in the field of oncology:

*“The best data so far is in oncology...looking at pharmacogenetics, is in looking at toxicity. And so there is good data that checking for UGT for instance with irinotecan can pretty much guess who’s gonna get the most toxicity for that drug.*

*Also with 5-FU. And then tamoxifen is still a real evolving story, but we do know that genetics can determine metabolism. Hasn't shown clinically to be meaningful yet. So I think there's a lot of potential and it's a worthwhile – a very worthwhile project.” (Respondent 582)*

Providers further explained the value in studying clinically relevant gene-drug pairs across the U.S. in increasing popular use of pharmacogenetic testing.

7. *Pharmacogenomics education – public and patients:* Comments related to whether informant feels there is a need for or value in improved patient and public education in genetics and pharmacogenomics. A majority of healthcare providers expressed the importance of educating the patient community about pharmacogenetic test benefits, results, and general information. One respondent mentioned how combined efforts in education both patients and providers is important for the uptake of pharmacogenetic testing:

*“...Some misconceptions among patient populations, and some of them are well-founded, because in the past genetic testing may have been used for really unethical or inappropriate uses, so there are populations that are very sensitive, cautious, and need reassurance that in face these kind of testing mechanisms are for their benefit. And so I think one of the things will have to happen is education, not only of provider but of patient populations.” (Respondent 700)*

Furthermore, most healthcare providers felt that it was their responsibility to translate pharmacogenetics information into a format that is understandable to their patients.

8. *Pharmacogenomics education – providers*: Comments related to current knowledge, educational priorities, and preferred information sources for providers to self-educate. This theme also includes comments related to awareness of available pharmacogenomic tests and understanding of pharmacogenomic concepts. Healthcare providers expressed how there exists a lack of formal education and training in pharmacogenetics and its applications for clinical use. They further described that educational needs can be met through continuing medical education (CME) courses. For example, CME courses are required for physicians, but are not always made available to nurses. One nurse suggested an educational approach that could be successful in informing nurses about pharmacogenetics:

*“Continuing education, a lot of times nurses, well from a nursing perspective we don’t always get to do those, so like online CEUs (continuing education unit) for that would be excellent, where you could go online and read about it, and then do questionnaire and get like a CME credit.” (Respondent 692)*

In terms of self-educating, respondents described various educational venues that they utilize such as: scientific meetings, CME courses, U.S. organizations (i.e. American Academy of Neurology, American Pain Society, American Cancer Society), major journal literature (i.e. Journal of American Medical Association), and colleagues.

*“...We look to people doing basic science research to find information. We kind of expect that a corporation will make the best financial use of that they can, and we*

*look to people doing academic medicine to figure out really who should be getting the test [genetic test] and who shouldn't." (Respondent 933)*

9. *Pharmacogenomic experiences*: Comments related to providers experiences using pharmacogenomics tests in clinical practice. Some healthcare providers talked about their experience with pharmacogenetics:

*"I worked as an oncology nurse for five years out in Oregon under the OHSU [Oregon Health and Science University] umbrella. We saw a lot of patients where we would do genetic testing for chemotherapy response for their tumors."*

*(Respondent 100)*

*"I mean 5-FU, Irinotecan are the two drugs that are probably number one for us being, for us knowing about it [pharmacogenetic testing]. So whenever I start a patient on those I always think about it [pharmacogenetic testing]. The problem is getting paid for it, and getting the answer soon enough to be of use." (Respondent 376)*

10. *Pharmacogenomics general – enthusiasm*: Comments related to informants' overall level of interest or enthusiasm about pharmacogenomics testing:

*"If I put on my hat as a collaborator in the research world – which I'm not a researcher by any stretch of the imagination, but I'm interested in the research – how our small clinic and our small population here, our community here could help make the difference of just learning more information about this, to benefit*

*from it, I think it's very exciting. I think it's worthwhile to sort of embark on that endeavor." (Respondent 781)*

*"I'm all for it. I think it's a great idea. I don't really know much about the issue or the details of what it all entails as far as how do you take individuals that are suited for it, but I think it's a great idea." (Respondent 692)*

*"Oh, my take is that I think they [pharmacogenetic tests] have a tremendous potential benefit. Obviously I'm a radiation oncologist, but over 50% of our patients are joint patients who also get chemotherapy, and in fact the response or the mechanism by which they metabolize the by-product of their chemotherapy can tremendously impact my radiation treatments. So I'm very excited to see progress and more testing."*

*(Respondent 700)*

These quotes highlight the support pharmacogenetics has in the medical community.

11. *Pharmacogenomics – patient views*: Comments related to perceived opinions about how patients and members of the public likely view or think about pharmacogenomics. Healthcare providers commented about how patients will have issues of confidentiality, privacy, and finances. In their understanding, these issues come from how patients view their genetic information as reflection of



oneself and that it is personal. Furthermore, healthcare providers explained how finances could play a role in decision-making:

*“Well I think that the...even though in the old days one of the decision points wasn't cost, now that will be. And the reason is as much as we hate to admit it, one of the stressors and one of the points for patients to make decisions is financial burden.”*

*(Respondent 700)*

Respondents also shared the opinion that some patients are just going to refuse the use of pharmacogenetic testing for their own personal reasons. Examples of these are as follows:

*“...I have some [patients] who are going to fight any test you give them. There are some that don't care.” (Respondent 347)*

*“..There's some skepticism with testing here. You know, all the time I do pulmonary function testing on people and it's pretty concrete and easy to interpret, and people all the time fight that. They'll smoke and say 'oh, I don't have any emphysema changes,' or anything like that. So I think some people would, as far as patients they'd say that's great information for me, but there would be some who would put up walls.” (Respondent 347)*

A cultural factor was mentioned by one provider:

*“A lot of it has to do with culture. They don't...they won't do something unless they absolutely feel that it's necessary. Like it's an emergency then they need to*

*get this done or something bad's gonna happen. Especially with our population [CSKT]."*

*(Respondent 692)*

12. *Pharmacogenomics risks*: Comments about the risks of pharmacogenomics tests to the patient or the provider. Concerns have surfaced regarding employers or insurance companies accessing genetic data. Healthcare providers mentioned how the risk of incidental findings may stem from initial benefits of an individual using a pharmacogenetic test.

*"Insurance companies getting ahold of the information is the big thing. I have my own personal beliefs on insurance but that's not what this interview is about. But I do believe that they [insurance companies], in the...the way that they manage health care for the people that they are supposed to be taking care of, they've actually caused harm and have done better at managing their stock holders' interests rather than the patients', and they'll use information against the patient rather than for the patient's benefit."* (Respondent 100)

Another major risk that was mentioned by several respondents was the issue of pharmacogenetic tests being substituted for clinical judgement. This risk stems from pharmacogenetics not resulting in their proposed benefits.

*"We get excited in the medical field about something that seems like it's going to be, you know, life-changing, in terms of how we do things, and it turns out not so much, or what we thought was going to happen turns out it was the opposite, or,*

*you know, we've all lived through those kinds of big changes. So there's always that potential risk.” (Respondent 781)*

In contrast, some healthcare providers did not have any immediate knowledge of risks associated with pharmacogenetic testing.

13. *Pharmacogenomics test – important attributes*: Comments about important test-related attributes that the informant would consider in ordering decisions. This theme also includes comments related to ordering process preferences as well as patient-attributes that would affect pharmacogenomics test ordering decision. The idea of a pharmacogenetic test in form of a panel that could analyze multiple genes was asked. Healthcare providers were ok with this concept as long as panel proved useful, was accompanied with interpretation materials, was affordable, and had a quick turn-around time.

*“You'd want to get them [patients] treated. You wouldn't want to wait for a turn around for results. We want to start treatment right away...” (Respondent 692)*

Healthcare providers also stated that one important attribute of implementing a pharmacogenetic test would be for it to be similar to other blood tests already established in the clinic. One respondent mentioned that ordering of a pharmacogenetic test should be:

*“As easy as possible. Honestly it'd be nice if...we do blood draws all day, every day. It would be nice if all the labs, like we go through Kalispell Regional, if they were set up through this program. It does...I don't want, it would make I think a lot of nurses and doctors not use it as much if they had to package it up separately*

*and send it out differently, you know it's something that took a lot of extra time.”*  
(Respondent 543)

14. *Pharmacogenomic test – result preferences*: Comments related to providers preferences for pharmacogenomic test results. There were variable responses by healthcare providers in their preference in what pharmacogenetic research results should contain. It ranged from respondents who didn't have much background in genetics or pharmacogenetics that opted for just the interpretation of results, while more informed respondents requested an all-inclusive report of results. One healthcare provider went in detail to what information they would like included in the results.

*“...Anything that bears on the metabolism of the drug, not only the rate but the differences like the metabolites, other substrates or inhibitors. But then you want to know what's the – how do I put this – it's not something we can know yet I think. Which receptors are really significant in the treatment of this and what's their sensitivity and level of disregulation?”* (Respondent 179)

Another specified result preference was to provide the relevance of genetic information findings was to commonly used drugs in healthcare.

15. *Provider context*: This theme was created to identify the location (i.e. Missoula, MT; Polson, MT) and tribal affiliation status of the informant.

16. *Ranking justification*: This theme includes all comments related to the card exercise where informants justified category rankings of three examples of pharmacogenetic tests in order of least important to most important. This theme also includes comments that provide insight into whether decisions were based on the informant's clinical experience or on principles of medical ethics. Comments also include preliminary justifications in the event that the informant changed ordering during the exercise. Many healthcare providers initially commented on the equal value of each of the three pharmacogenetic tests for different reasons before ranking them. Healthcare providers ranked according to main need for test in their practice, validation of tests, and clinical utility. All but one of the healthcare providers ranked the pharmacogenetic test for drug efficacy in their top two choices due to the potential of it being able to eliminate the process of trial and error of effectively prescribing anti-depressants.

At times, pharmacogenetic tests for drug efficacy and adverse events were grouped together as most valuable in healthcare. One respondent explained:

*"I would put efficacy and adverse events as being equivalent kinds of information. You know, any medical treatment is based on a ratio – weighing a benefit to risk. Anything that can make that ratio better is helpful to us clinically. And so being able to choose based on efficacy or likelihood of adverse events maximizes that ratio for us." (Respondent 933)*

When providers were asked to choose only two pharmacogenetics tests that they would want implemented in their clinics, the test for dosage and monitoring was commonly dropped. Most healthcare providers felt that there was already an

effective approach to dosing and monitoring that, if need be, could be accomplished on their own without a test. One provider was asked which pharmacogenetic test they would drop, their response was:

*“Dosage, if we know we need a bigger dose we’ll get there eventually with or without a genetic test.” (Respondent 743)*

Another respondent explained their reason for choosing to drop pharmacogenetic test for dosage and monitoring:

*“The warfarin example is one that I think is, we probably don’t even need the drug testing. I’ll know in five days what the right dose would be. And by then we probably don’t even have the test result back, and we’ve gotta start, we’ve gotta start that day we know they’ve got a clot.” (Respondent 376)*

There are various rankings of these pharmacogenetic tests and the reasons are variable amongst physicians. This suggests that implementation of pharmacogenetics will be site and discipline specific.

17. *Rural community specifics*: Comments identifying factors that are unique to, or particularly present or absent in rural communities. Main comments related to this theme explained how Montana is “sheltered” from a lot of new advances in medicine. Furthermore, healthcare providers explained that people from rural areas are more resistant to new therapies relative to their experiences outside of Montana. One provider spoke on several issues for pharmacogenetic testing in rural areas:

*“I would think small towns would be a little bit more user friendly for the patient and the pharmacist. But so much of it is driven by third-party payers, whether they have to get mail order or not, drives where they’re gonna get their drugs. So it actually, I think, depends more on the third-party payer.” (Respondent 961)*

Some provoked questions as to how insurance companies and cost will affect rural communities in getting access to pharmacogenetic testing. Overall, there were not many comments related to this theme, but it still provided valuable insight into rural considerations for the implementation of pharmacogenetic testing.

18. *Tribal community specifics*: Comments identifying factors that are unique to, or particularly present in or absent from tribal communities. Notable issues unique to tribal communities were expressed by healthcare providers as historical trauma, negative history with research, poverty, lack of education, lack of resources, and high incidences patient non-compliance. These were mentioned as issues that limit the uptake of pharmacogenetic testing. Another issue revolved around the way tribal people view their genetics. One provider described this:

*“And in some regards people [tribal] relate the two [genetics and cultural identity], that your genetics is part of your cultural identity, and therefore there is always the potential that if we’re analyzing one, we’re analyzing the other, and therefore they’re both able to be at risk.” (Respondent 781)*

In contrast, healthcare provided enhancers that exist in tribal communities that are unique to them. For example, tribal communities have two resources for

healthcare, Indian Health Services and Tribal Health. To this end, providers mentioned how it would be of value to get these two healthcare entities on board to increase opportunities for testing implementation. One respondent emphasized this point:

*“Tribal Health is a huge thing. Indian Health Services is a huuuuuge entity. Powerful. Across the nation.” (Respondent 663)*

Furthermore, providers commented that it would be an advantage to educate “*opinion-makers*” (i.e. tribal elders, tribal council, and THHS department heads). However, in educating tribal patients it has proven difficult to educate them in groups. This suggests that there may be a need to develop different modes of educating this patient population.

19. *Trust*: Comments related to patient or community trust toward providers, genetics, or other entities and concepts such as the US government. May include both current level of trust as well as comments related to building and losing trust. In terms of community trust, the majority of healthcare providers discussed the incidence of past negative research conducted with AI/AN populations and how this role plays into the issues of trust:

*“That willingness to trust may be more of an issue than in some communities [non-native] who haven’t experienced that [research abuse]. Even though this particular community [CSKT] hasn’t, I don’t think, experienced any direct...trauma, in the sense of genetics and testing and experimentation and research...But because native people in general have, we all sort of identify with*



*that and we don't want that to happen to us [native people]. I think that's a real and reasonable fear and anxiety that people [native] have.” (Respondent 781)*

*“...there's quite a lot of historical trauma with Native Americans trusting primarily governments and authority figures because of the way history has played out for us Native Peoples.” (Respondent 775)*

These data emphasized the importance of reassurance by researchers that they will honor their intentions of only looking at genetics related to drug response and avoid the opportunity of looking more broadly.

#### 3.4. DISCUSSION

The purpose of this study is to evaluate the potential value of pharmacogenetics research in healthcare to address health inequalities amongst the CSKT community. This study used interviews to explore healthcare providers' knowledge and opinions of pharmacogenetics research, and its translation into rural Montana healthcare systems. Healthcare providers discussed their understanding of general genetic concepts and how they relate to the field of pharmacogenetics research and its associated future clinical utility. The majority of participants involved concluded that pharmacogenetics research would be beneficial in its translation into the clinic. Amongst participants, concerns of cost issues, ethical considerations, privacy issues, mistrust, and reluctance due to misconceptions and lack of education were the main barriers to the implementation of pharmacogenetic testing. Evidence shows that these concerns are common amongst the medical community and have been acknowledged in previous studies investigating the

opinions and views about pharmacogenetics of healthcare providers from U.K. and U.S. populations (Fargher et al., 2007; Roth et al., 2011)

The views from the healthcare professionals living in rural northwestern Montana were evaluated to assess knowledge gaps, barriers and enhancers, and cultural factors specific to this region of Montana in the uptake of pharmacogenetics. Healthcare professionals interviewed in this study represented a diverse background and range of disciplines. This provided sources of information from providers of tribal affiliation, providers with experience in serving rural and tribal populations, and providers familiar with socioeconomic barriers and enhancers in rural and tribal areas. Furthermore, views from various healthcare professionals provided information on clinical utility and educational needs across disciplines. One main concern of healthcare professionals was that cost issues may arise if pharmacogenetic testing was not adopted by healthcare entities, such as Tribal Health, which are the main sources of healthcare in AI/AN communities and provide them with free services. One healthcare provider explained how free healthcare for the CSKT community was a unique characteristic of tribal populations because the U.S. government made an agreement with AI/AN communities that they would provide them with health amenities. Other cultural barriers mentioned by healthcare professionals were issues of mistrust due to historical events related to genetics research in AI/AN populations that resulted in misuse of tissue specimens and power. This issue of mistrust comes up often in literature associated with AI/AN participation in research and reiterates the importance of working *with* tribal groups. For example, misuse of tissue specimens took place when the Havasupai tribe of Arizona agreed to participate in a genetics study with Arizona State University to investigate the

high incidences of type II diabetes in the Havasupai community (Harmon, 2010). Through understanding the negative history behind genetics research with AI/AN populations we are better equipped in addressing these cultural barriers. Another cultural barrier highlighted in interview data was lack of genetics education that may result in opposition to pharmacogenetic testing and therefore prevent CSKT community members from receiving the benefits of this service. However, there exist enhancers that can help overcome these barriers such as educating tribal leaders (i.e. Tribal Health department heads, Tribal Council, and Cultural Committee Members) about pharmacogenetics and the potential clinical utility of pharmacogenetic testing. This would be wise in that these tribal leaders are the initial decision-makers of the CSKT community and their support in this research increases the acceptance of pharmacogenetic test implementation.

This study used exploratory qualitative methods to address healthcare provider views in pharmacogenetic research, and furthermore to assess the feasibility of implementing pharmacogenetic tests into Tribal Health clinics. Knowledge gained from interviews will assist in whether pharmacogenetic testing will be accepted and if so, develop strategies to create an implementation model that fits with rural and tribal healthcare facilities. Gathering views and attitudes from healthcare professionals is necessary to determine how best to deliver pharmacogenetic testing services and the impact of these testing services in rural and tribal communities.

## CHAPTER 4

### PATIENTS' VIEWS ON PHARMACOGENETICS AMONGST THE CONFEDERATED SALISH AND KOTENAI TRIBES

#### 4.1. INTRODUCTION

Since the completion of the Human Genome Project, there have been increased efforts to learn more about genetic variation in relation to health issues. Significant advances in knowledge about pathways affected by genetic variation have provided new ways in understanding humans. Pharmacogenetics is the field of study that focuses on variation in drug response due to genetic factors in different populations (Roses, 2001; Vesell, 2000; Ventola, 2011). The benefits of pharmacogenetics include the potential to identify sources of the aforementioned interindividual variability in drug disposition and response in efforts to create safe and effective ways to prescribe medications through the use of pharmacogenetic tests (Eichelbaum et al., 2006; Kitzmiller et al., 2011; Crews et al., 2012; Johnson et al., 2012). Furthermore, an added goal of pharmacogenetics research is to evaluate genetic variation in all world populations to better understand interindividual variability in drug response (Ventola, 2011).

However, American Indian and Alaska Native (AI/AN) populations in the U.S. have traditionally not been included in pharmacogenetics research; and therefore, may be overlooked in the advancement of personalized medicine. Although pharmacogenetics offers opportunity to improve patient and population health outcomes, indigenous communities may differ in their judgement about its priority compared to other health research and world populations. Currently, only a few studies exist that explore the lay persons views about pharmacogenetics research from U.S. and U.K. European, African American, and Asian populations (Almarsdóttir et al., 2005; Bevan et al., 2003; Condit and Bates, 2005). In order to successfully conduct pharmacogenetics research and facilitate its translation into Tribal Health clinics, it is of value that discussions exist

amongst the CSKT community. There is no clear model of how this is to be achieved; however, the right place to start is with our partner communities to develop a model that best fits their community needs and priorities. Therefore, to assess the perceptions and opinions of AI/AN participation in pharmacogenetics research and its translation into the clinic, we have worked with the CSKT to identify barriers and gain information about the acceptability of pharmacogenetics research and pharmacogenetic testing, and discuss strategies to disseminate research results.

In this study, we have used the qualitative methods of focus groups CSKT volunteers who receive their healthcare at Tribal Health facilities. Focus groups are an effective method that allows open discussions with participants to as well as opportunities for the researchers' to ask for elaboration on participant responses in relation to other participants (Morgan, 1996; Powell and Single, 1996; Farnsworth and Boon, 2010; Duggleby, 2005). For these reasons, we chose to use focus groups as a way to assess attitudes of the CSKT community towards pharmacogenetics research, pharmacogenetics testing, and input regarding dissemination of research findings. This method allows researchers to encourage people who may feel intimidated by, or unwilling to, participate in individual interviews, who have trouble reading and writing, or who feel they "have nothing to say." On-going consultation with tribal authorities and the CPAC during the research process ensured that the focus group guide was informed by local knowledge and expertise, and implemented appropriately as discussed in Chapter 2. The focus of this study was to generate discussions that address the ethical concerns of pharmacogenetics research, how to develop pharmacogenetic studies in the CSKT community, and how,

and when, should pharmacogenetic study results be returned back to the CSKT community.

## 4.2. METHODS

### 4.2.1 STUDY SUBJECTS

Approval for this research was obtained from the CSKT Tribal Council, the CSKT Tribal Health and Human Services Department, and the Institutional Review Boards (IRBs) of the University of Montana and the University of Washington. Prior to initiating any research procedures, written consent was obtained using forms approved by the IRBs. To date, CSKT subjects 18 years and older (n=7) were recruited for participation in focus groups by CPAC members and University of Montana researchers. Focus groups were stratified by age: <40 years of age (n=4) and  $\geq$ 40 years of age (n=3). All participants were female.

### 4.2.2 FOCUS GROUPS

Focus groups were audio recorded and observational field notes were taken for thorough interpretation of views on pharmacogenetics research. The moderator's guide described in Chapter 2 that was developed jointly by researchers and community members was used. The focus group is a work-in-progress as we have held only 2 focus groups thus far. In one case, a participant arrived later and therefore we performed an interview. This interview data will be included with the data from the focus groups. The focus groups last approximately two hours. In conducting the focus groups, the moderator

welcomes the participants and discusses ground rules concerning confidentiality and informed consent. All focus groups were assigned a color in place of their name to de-identify participants during the audio recording. During the focus group, members of the group were asked a series of open-ended questions revolving around three main topics: 1) the field of pharmacogenetics 2) clinical utility of pharmacogenetic tests 3) dissemination of results back to community. When appropriate, facilitators used storytelling as a means of communicating focus group topics to the group members. An important focus of the discussion was to determine whether pharmacogenetics research provides benefits applicable to the needs of the CSKT community. Furthermore, focus group participants were asked to identify potentially culturally-relevant strategies to implement pharmacogenetic testing. Finally, focus group participants were asked questions that addressed the issue of disseminating results and how best to share research results in an understandable format.

#### 4.2.3 QUALITATIVE ANALYSIS

Initial analysis of focus groups included content analysis of handwritten notes taken at time of focus group discussions. Themes that emerged from these notes are described in the results section. Further analysis worked to group responses based on meanings, themes, and patterns that are included in the moderator's guide during the analysis process. Research experts and trained graduate students worked together to develop a coding thematic scheme to assess views of the CSKT patient community using the Dedoose © qualitative analytical software package (Los Angeles, CA). The full study team will review and discuss all summary results with our CSKT community partners



## 4.3 RESULTS

### 4.3.1 FOCUS GROUP SUMMARY

Results of the focus groups are preliminary as we have only completed 2 focus groups (7 subjects total). Our intent is to recruit approximately 30 CSKT members. The first two focus groups had smaller than anticipated participation (3-4 people vs. the intended 6-8 people); therefore, more focus groups may have to be conducted with fewer people. As described earlier, the format of the moderator's guide was divided into three main categories and results will be summarized relative to these categories: 1) the field of pharmacogenetics , 2) clinical utility of pharmacogenetic tests, and 3) dissemination of results.

### 4.3.2 FIELD OF PHARMACOGENETICS RESEARCH

Participants' views in this topic were related to knowledge of pharmacogenetics research, attitudes towards pharmacogenetics research (enhancers and barriers), and cultural factors.

- *Knowledge of pharmacogenetics research:* Comments related to how knowledgeable the participants currently feel about pharmacogenetics. When participants were asked whether they had heard that genetics played a role in drug response, more than half responded "yes" and needed no further clarification. In particular, a few participants began talking about their experiences with pharmacogenetics such as sensitivities to pain medications.

- *Attitudes towards pharmacogenetics research:* Participants discussed views about this type of research in non-CSKT populations as well as CSKT populations. Participants were asked questions regarding views on pharmacogenetics research, participation in this type of research, and materials used for pharmacogenetic research studies. Positive attitudes were a consensus in conducting research in both populations and participants described how pharmacogenetics is beneficial and needed in order to move research forward. Some participants commented on their willingness to be a part of this type of research for the betterment of future generations of the CSKT community. Some enhancers described by participants were to provide education about the research project to increase uptake of pharmacogenetics research. This education should involve all levels of the community (i.e. tribal council members, tribal health affiliates, lay CSKT community). Another enhancer of pharmacogenetics research included working with trusted Tribal Health and Human Services physicians, CSKT Tribal Council, and both the Salish and Kootenai Cultural Committees to help earn the trust of the CSKT community. One participant made it clear that throughout the research project the researchers should keep them [CSKT community] involved and “be transparent all the way through.” Barriers that could obstruct or limit the participation of CSKT members in pharmacogenetics research included lack of education.

- *Cultural factors:* Participants were asked questions about cultural concepts to keep in mind when conducting pharmacogenetics research. Participants' comments included consciousness that there are three different tribes on the Flathead Indian Reservation, and that there exist different beliefs and cultural practices amongst them. Furthermore, researchers should be aware of CSKT people who still believe in their traditional medicines and do not practice western medicine. Cultural enhancers include working at the pace of the CSKT community and respecting their individual cultures. Participants also described how there were many barriers with the elders in the CSKT community who don't believe that any type of research is necessary. We also queried participants about the types of information researchers may gather, such as medical records, completed surveys, questionnaires, or interviews, and samples of blood or other parts of the body. When asked questions concerning these forms of information, participants felt that it would be fine for researchers to have access to their medical records, but would like an explanation and to give permission beforehand. Others felt that the use of their medical records was a sensitive issue and had concerns about how information would be used or the extent of access to this information. A majority of participants felt that the use of surveys, questionnaires, and interviews as a tool for gaining information would be more appropriate because they preferred face-to-face contact with researchers. In terms of requesting blood samples or other tissue samples, attitudes were split. Some felt that it would be alright to give blood and a couple of participants had mentioned that a request for medical records was more sensitive than giving a blood sample.

Others were more hesitant to give a blood sample because they felt it was very personal and were unsure of its implications.

#### 4.3.3 CLINICAL UTILITY OF PHARMACOGENETIC TESTS

Participants' views on this topic were explored related to attitudes towards available genetic tests, barriers for implementing genetic tests into the clinic, and ways to remove these barriers.

- *Attitudes towards genetic tests for warfarin and tamoxifen:* Participants discussed positive factors about the adoption or use of available specific pharmacogenetic tests for warfarin and tamoxifen. One participant reported that it would be “we’d be going backwards” if we did not to take advantage of available pharmacogenetic tests. One benefit of pharmacogenetic testing was the possibility that Tribal Health would be saving money by limiting the prescription of drugs that aren’t helping. Specifically, one participant mentioned how the benefit in taking a tamoxifen test would save time and money, insisting that time would be saved in prescribing and money would be saved in a therapy that doesn’t work. Participants were also asked to choose which pharmacogenetic test they preferred if they could only afford one in Tribal Health. Some chose the tamoxifen test over a warfarin test and justified this choice partly due to the “seriousness and scariness of the disease [breast cancer]” associated with the tamoxifen test. Others had mentioned choosing the test by determining which would have the higher need amongst the community in terms of patient numbers as well as which would be most cost-effective.

#### 4.3.4 DISSEMINATION OF RESULTS

Participants' views in this topic were related to attitudes towards kinds of research information to share and best ways to share research findings.

- *What kind of research information to share:* Participants wanted research information pertaining to kinds of medications being focused on, impact of the research, and results elicited from the research to be shared publicly with the CSKT community. One participant mentioned that the return of results should highlight the benefits to the community and future generations.
- *Best ways to share information:* Participants expressed views about the best ways to share research project information and results. Participants identified several strategies in sharing information with the CSKT community. Some of these strategies include: go through Char-Koosta News to report research information, community meetings, utilize TV and radio news, presentations at Salish Kootenai College (CSKT tribal community college), and use of pamphlets and written materials.

#### 4.4 DISCUSSION

Focus group data from CSKT members are still in the initial stages. Nevertheless, emerging themes reveal significant insights pertaining to the views and attitudes of CSKT members about pharmacogenetics research, pharmacogenetic testing, and sharing of research results. CSKT views were overall positive in acknowledging the potential

benefits of pharmacogenetics; however, explanations of implications of pharmacogenetics were needed. Potential harms of pharmacogenetics were a huge concern of participants and some of these concerns were rooted in misconceptions genetics research. This suggests a lack of knowledge in the area of genetics research, which can be improved through educational efforts. Furthermore, CSKT participants expressed enthusiasm for the use of pharmacogenetic tests in providing therapeutic efficacy for severe disease cases. This provides insight to priority needs within the CSKT community and perhaps implementing a pharmacogenetic test around this priority may increase uptake of pharmacogenetics into Tribal Health clinics. In contrast, some CSKT members mentioned that cultural barriers exist amongst the broader CSKT community that may limit the use of pharmacogenetic tests by tribal patients. One concern was that elders have a strong belief in traditional medicines over westernized medicine and therefore may be opposed to using available testing services. However, one participant mentioned that through consistent discussions with the older populations, this may facilitate a more positive outlook on pharmacogenetics research.

In regards to developing strategies to facilitate the return of research results, CSKT members provided various avenues of disseminating results to the broader CSKT community. In previous studies working with AI/AN populations, researchers failed to share research findings with the community understudy. Thus, discussions about dissemination strategies are a key component in changing the shape of traditional research and provide a foundation for trust to be established amongst researchers and AI/AN communities.

In summary, this research will provide insight into the obstacles that exist in implementation of pharmacogenetic research and pharmacogenetic testing (i.e. Tribal Health's available resources, guidance for providers in the use of pharmacogenetics tests, and cultural sensitivities), and how these barriers may be overcome to deliver pharmacogenetic testing more broadly to the CSKT community. Furthermore, focus groups data will provide guidance on how best to develop culturally relevant and appropriate tools for dissemination of pharmacogenetic research results back to the CSKT community. The next steps for this project are to complete focus groups and analyze focus group data. Through this research we hope to change how drugs are administered in AI/AN communities through implementation of pharmacogenetic testing.

CHAPTER 5

CONCLUSION



The focus and intent of my thesis research was to work in partnership with the CSKT community to evaluate the value of pharmacogenetics and identify limiting factors that may interrupt its implementation into local healthcare facilities. To address this goal, I utilized a variety of CBPR methodologies to (1) engage and educate CSKT community members about the potential benefits of pharmacogenetics research and its applications, (2) evaluate healthcare professional, and (3) CSKT community views of pharmacogenetics research and its translation into the clinic. These CBPR methods are essential in understanding barriers and enhancers for implementing pharmacogenetics into the CSKT community. Results obtained from this thesis will continue to inform and guide this research project in a culturally appropriate manner so that research goals are relevant to the health issues of the CSKT community. In addition, views of healthcare providers and the CSKT community will prove valuable in future implementation of pharmacogenetic testing and dissemination of research project findings.

Progress in the field of pharmacogenetics has provided evidence for its potential benefits in personalizing medicine. Knowledge of major genetic variants in CYP450 drug metabolizing enzymes and other enzymes (i.e. thiopurine methyltransferases (TPMT), UDP glucuronosyltransferases (UGTs)) has resulted in recognition of their clinical relevance in patient drug response (Crews et al., 2012; Eichelbaum et al., 2006; Evans and Relling, 1999). Genetic variability has the potential to result in adverse drug reactions. In 2006, the FDA recorded adverse drug reactions as the fourth leading cause of death in the United States. Pharmacogenetics provides the opportunity to identify patients at high risk of adverse drug reactions, as well as improving drug efficacy, through understanding and discovering mechanisms underlying interindividual

variability. The gene-drug pairs that have been characterized to date are already being adopted by FDA and incorporated into drug labeling along with the CPIC developing prescribing guidelines. For example, TPMT testing is recommended before starting treatment with azathioprine (Imuran) because of known blood toxicities of patients with TPMT deficiency (Eichelbaum et al., 2006). Another example is HLA-B (major histocompatibility complex, class I, B) testing that is recommended before starting carbamazepine or abacavir treatment due to known HLA-B variants that can induce Stevens-Johnson syndrome and other severe hypersensitivity reactions (Kitzmiller et al., 2011). These aforementioned examples show evidence of interethnic variability in pharmacogenetic variability. Combined efforts in discovering sources of interindividual variability and how this varies further across ethnic groups is now a research topic of interest. So far, population studies in pharmacogenetics have largely included European, Asian, and African populations, with few studies targeting indigenous groups (Fohner et al., 2013; Jaja et al., 2008; Limdi et al., 2008). To ensure that pharmacogenetics reaches its optimal clinical utility, pharmacogenetics research should include all members of society and the extent of pharmacogenetic variability across ethnic populations should be studied. Therefore, the broad goal of this thesis was to include AI/AN populations in pharmacogenetics research and to determine and evaluate the value of pharmacogenetics in this population.

Issues of mistrust exist when conducting research with AI/AN populations due to past abuses of genetics research that were described in the Introduction. Fortunately, in recent years there has been a demand by both community and public health researchers for new research models that encompass both community and researcher expertise. One

research model that has emerged from these demands is CBPR, which promotes community involvement at every stage of research and provides a framework to conduct collaborative research. The growing support and success of CBPR in health research stems from the acknowledgement of the negative history of research conducted with AI/AN communities and recognition of the value of community involvement (Thomas et al., 2009; Boyer et al., 2011). The goal of implementing a CBPR approach is to work productively with our CSKT partners to develop meaningful health outcomes that take advantage of community strengths in efforts to increase intervention sustainability.

The first step was identification and recruitment of key informants of the CSKT community to comprise the CPAC. The CPAC represents a diverse sample of the CSKT population and helps to provide tribal input to the research process, develop research materials, and recruit for focus groups. Monthly meetings are held with the CPAC and university researchers to discuss research updates and educate the CPAC about pharmacogenetics to create a space for research dialogue. Along with the CPAC members, efforts have been made to engage and educate the broader CSKT population through workshops, presentations, and the Char-Koosta newspaper. The impact of these aforementioned educational tools was evaluated through surveys and on-going consultations with the CPAC. The information gained from these surveys suggested that community members and CPAC members were retaining basic genetic concepts and using pharmacogenetics terminology properly. In addition, community feedback from surveys has also included comments related to areas of needed improvement that will help guide further educational ventures.

There exists limited published literature on investigating healthcare professionals' (Fargher et al., 2007; Dodson, 2011; Institute of Medicine, 2002) and patients' views (Lanie et al., 2004; Condit and Bates, 2005; Almarsdóttir et al., 2005; Emery et al., 1998) about pharmacogenetics research and its applicability in the clinic. In addition, there is no clear model on how to deliver testing services into healthcare facilities. In order for successful implementation of pharmacogenetic tests, there needs to be discussions with healthcare professionals, patient community, and policy makers to address issues involved in integrating testing services into healthcare facilities. To address this lack of dialogue in pharmacogenetics research, we have incorporated qualitative methods to explore the views of healthcare providers and CSKT community members.

Healthcare provider interviews were conducted to explore provider views about potential benefits and harms associated with pharmacogenetic testing, its acceptability by local healthcare facilities, and the evidence and available resources needed to integrate pharmacogenetic testing into common healthcare protocols. Many providers agreed that pharmacogenetic testing holds potential clinical utility; however, barriers exist that may prevent its implementation into the clinic. Some barriers mentioned were issues of cost, trust, ethics, and education. Although these barriers exist, healthcare providers mentioned enhancers such as educating both healthcare providers and patients about pharmacogenetics to relieve any misconceptions. Healthcare providers also described the importance of respecting the culture of CSKT community members and recognizing that past abuse of research power has resulted in mistrust. Therefore it's important to explain how this research project differs to build trust.

Focus groups were conducted with CSKT community members that discussed three major concepts: (1) pharmacogenetics research, (2) pharmacogenetic testing, and (3) dissemination of research results. The research results of the focus groups are preliminary but there is a general enthusiasm for the potential benefits of pharmacogenetics research in local healthcare facilities. Comments related to pharmacogenetic testing were positive and participants felt that if they are available they should be utilized. Results also suggest that there is still a need for education in the area of pharmacogenetics and this lack of knowledge may create barriers to the participation of CSKT community members in pharmacogenetics research and testing. Furthermore, in adhering to the principles of CBPR it is important that research findings be reported back to the broader CSKT community. Focus group results highlighted several strategies that will be useful in ensuring that research findings are made public to the CSKT in an understandable and culturally respectful manner. A few examples of these strategies include presentations at SKC, discussion forums, and pamphlets. Results obtained from focus groups will be useful in determining unknown barriers and enhancers that exist in the CSKT community towards pharmacogenetics research.

In summary, this thesis has described the CBPR methods developed and utilized to work in partnership with the CSKT community in conducting pharmacogenetics research. In addition, CBPR has provided a framework to promote community involvement that will facilitate unique and relevant outcomes within the CSKT community. Because the traditional research approach, in which researchers have already developed preconceived research questions and design, has not been successful in working with AI/AN populations, this study has shown how CBPR has created

opportunities to build capacity amongst research partners, long-lasting relationships, and trust. Furthermore, qualitative research findings are the first steps in incorporating views, attitudes, and realities of stakeholders in pharmacogenetics research and contributing other viewpoints that exist in this field. Future work still needs to be done in completing focus groups, data analysis, and using this information to further guide this research.

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