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EQUITABLE PHARMACOGENETIC TESTING IMPLEMENTATION FOR RURAL AND UNDERSERVED POPULATIONS

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This work would not be possible without assistance from incredible people in my life.

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Equitable pharmacogenetic testing implementation for rural and underserved populations

Chairperson: Erica Woodahl, PhD

Pharmacogenetic testing has potential to transform healthcare, yet implementation strategies have been limited to major academic medical centers serving metropolitan communities and large health systems. In contrast, rural, community-based health systems are slow to implement these advances, threatening to exacerbate existing healthcare disparities for rural populations. A majority of Montanans live in rural areas, with unique challenges in providing access to pharmacogenetics.

We have established partnerships with three clinical sites who serve rural, underserved populations including American Indian, pediatric, and low socioeconomic status patients. We conducted a needs assessment for pharmacogenetic testing implementation by interviewing 48 key stakeholders. Interview questions were centered around participants opinions regarding pharmacogenetics and their perceived barriers and facilitators for implementation of testing. A codebook was created by analysis and organization of common themes.

Positive opinions on using pharmacogenetics to guide therapy were common. Perceived benefits included reduced time to symptom management, fewer adverse events, and improved adherence. Concerns expressed in similar studies based in larger medical centers were also present, including conflicts with reimbursement and test turnaround time. Unique concerns for vulnerable, underserved populations included equitable access based on socioeconomic status and sensitivity to culture and historical injustices, particularly for tribal people. Participants were enthusiastic about using telehealth to implement pharmacogenetics in these communities. This will provide an innovative strategy for pharmacogenetic testing and consultations.

Participants were eager to implement testing in their facilities. Many concerns can be mitigated with a strategic implementation plan targeted for underserved patients. Our model will implement pharmacogenetics using a telehealth delivery model centered at the University of Montana with outreach to rural health systems and providers. This has the potential to expand as new health innovations are translated into practice. Future work in this area will involve assisting partner sites with implementation efforts and measuring clinical outcomes related to testing services. Our study will help overcome the unique challenges in delivering pharmacogenetics to rural and underserved communities and we aim to provide a model for states with similar patient populations. Our goal is to pave the way for equitable access to pharmacogenetics for all.

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Chapter 1. An Introduction to Clinical Pharmacogenetics

1.1 Introduction to Precision Medicine and Pharmacogenetics

Historically, healthcare recommendations have been based on a “one-size fits all” treatment model, however, recent research and technological advancements have encouraged providers to alter the way they practice medicine. Precision medicine is a clinical approach that factors in patient-specific information to make diagnostic conclusions and treatment recommendations. Variables that may influence therapeutic approaches include environmental exposures, lifestyle factors such as diet and physical activity, social determinants of health, and genetics. Considerations in individual genetic variability give clinicians the ability make more precise conclusions about patient health, leading to better health outcomes [1]. After completion of the Human Genome Project in 2003, medical researchers have employed genomic studies to develop innovative healthcare advancements. Efforts have been made to develop to models for early disease detection, cultivate gene therapies, personalize therapeutics, and more [2, 3].

Several developments resulted from this achievement, including the Precision Medicine Initiative, an effort launched under the Obama administration to “revolutionize” medical practice by understanding mechanisms of disease progression and treatment. The Precision Medicine Initiative was renamed to the All of Us research program, a campaign aimed at ensuring precision medicine research and technology development are distributed equitably [4-6]. Genomic data generated from this initiative is to be used in developing new technologies for precision health advancements.

Knowledge in genomics and its influence on patient health has generated increased research in pharmacogenomics, an application of precision medicine that uses patient-specific genetic data to optimize treatment recommendations. First coined by Fredriech

Vogel in 1959, pharmacogenomics relates genetic data and to variable drug response and toxicity [7]. Variation in “pharmacogenes”—genes that encode proteins that influence medication response—can influence both the pharmacokinetics and pharmacodynamics of a drug. Pharmacokinetic pathways include pharmacogenes encoding drug-metabolizing enzymes such as cytochrome P450 enzymes (*CYPs*) and drug transporters such as the organic anion transporter protein (*OATP1B1* or *SLCO1B1*). Pharmacodynamic pathways include pharmacogenes encoding drug targets such as the vitamin K epoxide reductase (*VKORC1*) and the mechanisms of toxicities such as alleles in the human leukocyte antigen (*HLA-A* and *HLA-B*) genes. The Pharmacogene Variation Consortium (PharmVar) is a centralized repository of genetic data that assigns standardized nomenclature to pharmacogene variants—designated as “star alleles” [8, 9]. PharmVar uses information generated from the Pharmacogenomics Knowledge Base (PharmGKB) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) [10-12]. Collaboration between these three groups results in clinical function assignment of star alleles. The goal of CPIC is to facilitate the implementation of pharmacogenetics by prioritizing gene-drug pairs with the highest level of evidence and by publishing clinical guidelines based on peer-reviewed pharmacogenomic research from around the world. To assist in this process, CPIC provides guidance on assigning a predicted phenotype from pharmacogenetics test results and providing pharmacogenetics-guided therapeutic recommendations.

Pharmacogenetic testing gives providers an additional tool in choosing optimal medications and medication dosing. Pharmacogenetic test results are used alongside other patient-specific factors, such as medication history, weight, and kidney function, to determine therapeutic recommendations including dose reductions, medication selection, and drug class avoidance. Examples of medications with published clinical

guidelines are presented in Table 1.1; a complete list can be found on the Pharmacogenomics Knowledge Base (PharmGKB) [10].

1.2 Pharmacogenes: Genotype to Phenotype

Pharmacogenetic phenotypic assignments are made based on the combination of haplotypes in an individual, or the diplotype. Pharmacogenetic haplotypes are identified by star alleles with corresponding protein function (e.g., normal, increased, decreased, or no function). By convention, **1* haplotypes for pharmacogenes are considered normal function with subsequent star alleles—and their assigned function—designated sequentially (e.g., **2*, **3*, **4*). As an example, cytochrome P450 2C19 (CYP2C19) metabolizes up to 10% of medications including some antidepressants, antifungals, and antiplatelets (Figure 1.1) [13]. The *CYP2C19* gene is highly polymorphic, with almost 40 star alleles exhibit variable effects on function: normal (e.g. *CYP2C19*1* and *CYP2C19*18*), increased (e.g. *CYP2C19*17*), decreased (e.g. *CYP2C19*16*), and no function (e.g. *CYP2C19*2* and *CYP2C19*3*) [14].

Star allele diplotypes are then translated into phenotypes, which in turn, give predictions of the function of the proteins in a patient. In general, for drug-metabolizing enzymes, phenotypes are described as metabolizing status (e.g., normal, ultrarapid, intermediate, and poor metabolizers). For CYP2C19, a patient with a *CYP2C19*1/*1* diplotype is designated as a normal metabolizer (NM) as they carry two normal function alleles. A patient with a *CYP2C19*2/*3* diplotype—with two no function alleles—is assigned a poor metabolizer (PM) phenotype. A patient with a *CYP2C19*17/*17* diplotype result would be assigned an ultrarapid metabolizer (UM) phenotype due to two increased function alleles. Diplotypes with mixed function are interpreted based on the combined

functionality of each haplotype. For example, a patient with a *CYP2C19*1/*2* diplotype is designated as an intermediate metabolizer (IM).

Patients' designated metabolizer status are subsequently paired with a treatment recommendation based on variability in drug plasma levels. UMs will eliminate medication more quickly than average resulting in lower than expected drug concentrations, forgoing therapeutic benefit. PMs experience the opposite, causing increased drug plasma concentrations, and potentially increase risk of side effects. For example, a CYP2C19 pharmacogenetic-based dosing regimen for active parent drugs may recommend that UMs require an increased dose and PMs require a decreased dose. In either case, an alternative medication not primarily metabolized by CYP2C19 may be preferred. It is important to note, however, that these recommendations only apply to medications that are metabolized to inactive metabolites. Prodrugs are medications that need to be converted to active metabolites, therefore PMs would fail to achieve sufficient concentrations of the active metabolites, resulting in therapeutic failure. When applying pharmacogenetic test results to therapeutic recommendations, it is important to reference the CPIC guidelines for specific medications. A visual representation of genotype to phenotype to treatment recommendation can be seen in Figure 1.1. Further exploration into therapeutic recommendations is described in the next section.

1.3 Clinical Utility of Pharmacogenetic Testing

Pharmacogenetic tests give providers an additional tool to create individually tailored treatment strategies based on patient specific variability in pharmacogenes. Guidelines for pharmacogenetic testing treatment recommendations are published by groups such

as CPIC based on results from peer-reviewed research [11, 12]. CPIC designates each gene-drug pair with a level of evidence based on the strength of pharmacogenetic association. Gene-drug pairs with CPIC levels of A or B designations have sufficient evidence to support treatment recommendations guided by pharmacogenetic test results. Alternatively, gene-drug pairs with CPIC levels of C or D designations do not yet meet the threshold to support therapeutic recommendations based on pharmacogenetics. Of the 448 gene-drug pairs listed, 155 are level A or B, and 96 of these have published clinical guidelines with actionable clinical recommendations. Guidelines through CPIC are continuously updated based on the most recent data available.

One example of a CPIC level A guideline is for the commonly prescribed selective serotonin reuptake inhibitor (SSRI) citalopram, which is predominantly metabolized into less active metabolites by CYP2C19 and is used to treat patients diagnosed with depression and/or anxiety [15]. Based on phenotype results, CPIC offers recommendations for dosing and drug selection. Recommendations for NMs and IMs indicate citalopram is prescribed at the standard recommended dose (20-40 mg) because patients will likely experience normal therapeutic drug plasma levels. CPIC guidelines indicate patients who are identified as UMs should receive an alternative antidepressant medication not predominantly metabolized by CYP2C19 due to subtherapeutic drug levels. Alternatively, PMs may experience increased the risk of side effects due to higher than average predicted drug levels. Potential side effects of citalopram include nausea, vomiting, QT prolongation, increased bleeding risk, weight gain, and suicidal ideation [16]. In this case, CPIC guidelines recommend starting citalopram at 50% the usual dose (10-20 mg) or choosing an alternative medication not predominantly metabolized by CYP2C19. It is important to note SSRIs may take weeks,

or even months, to achieve maximum therapeutic benefits. Therefore, it is imperative to prescribe the correct medication and dose for patients as efficiently as possible to improve symptom management. In addition to CPIC guidelines, the FDA recommends CYP2C19 PMs receive a maximum dose of 20 mg of citalopram to reduce the risk of adverse events such as QT prolongation [17].

As mentioned earlier, variations in pharmacodynamic genes can also influence drug prescribing decisions. HLA-B plays a critical role in normal immune recognition of pathogens. Carriers of the *HLA-B*57:01* allele have an increased risk of subcutaneous hypersensitivity reactions when prescribed abacavir. The rate of hypersensitivity reactions among all patients starting abacavir is as high as 6% without preemptive pharmacogenetic testing with the risk being substantially different between carriers and noncarriers of *HLA-B*57:01*: 61% and 4%, respectively. Hypersensitivity reactions can be a multi-organ clinical syndrome, causing hospitalizations or even death in some patients. CPIC guidelines recommend patients who test positive for *HLA-B*57:01* are initiated on alternative antiretroviral therapy to mitigate this risk. The FDA also recommends *HLA-B* pharmacogenetic testing when initiating abacavir. Fortunately, there are several other options available for antiretroviral treatment of HIV. Recommendations for pharmacogenetic testing of other *HLA* alleles also exist for several other medications that may illicit hypersensitivity reactions such as carbamazepine, allopurinol, and phenytoin [18-23].

Sometimes variability in drug response can be influenced by multiple pharmacogenes. The drug warfarin acts to prevent clot formation in patients at high risk of stroke or other coagulopathies. CPIC guidelines for warfarin include *CYP2C9, CYP4F2, and VKORC1*. Warfarin is a racemic mixture, with S-warfarin as the active compound. Variation in

CYP2C9 and *CYP4F2* results in fluctuating S-warfarin exposure. Patients who carry *CYP2C9*2* and **3* alleles show a reduction in S-warfarin metabolism by 30-40% and 80-90%, respectively, are at an increased risk of bleeding events, and require lower starting doses to achieve therapeutic effect. Additionally, CPIC warfarin guidelines were updated in 2016 to include *CYP2C9* variant alleles more commonly in patients of African ancestry. These variants (i.e., *CYP2C9*5, *6, *8, and *11*) have shown to influence warfarin clearance and dose reductions of 10-50% are indicated to reduce bleeding risk. *CYP4F2* catalyzes vitamin K metabolism, removing it from the vitamin K cycle, and influencing the efficacy of warfarin. Including *CYP4F2* testing in warfarin dosing models has shown improved accuracy of dose predictions. Studies have shown patients who carry the *CYP4F2* variant rs2108622 require 8-11% higher warfarin doses than average, and CPIC guidelines state carriers should begin with an increased warfarin dose of 5-10% when initiating therapy. Finally, variations in *VKORC1* have shown to exhibit fluctuations in S-warfarin sensitivity. For example, some variants of *VKORC1* are associated with increased warfarin sensitivity and carriers require progressively lower warfarin doses. The algorithm provided by CPIC incorporates all three pharmacogenes mentioned in dosing recommendations.

1.4 Current State of Pharmacogenetic Testing Implementation in the US

Pharmacogenetic testing has the potential to transform the way medications are prescribed and testing programs have been successfully implemented in academic medical centers and large health systems serving patients in major metropolitan areas [24-27]. For example, some academic medical centers have established their own successful pharmacogenetic testing programs through the lens of implementation research. The University of Florida Health Precision Medicine Program (Gainesville, FL)

conducts pharmacogenetic testing consultations with patients through a pharmacist-led initiative [28]. St. Jude's Children's Research Hospital (Memphis, TN) has utilized preemptive pharmacogenetic testing in their PG4KDS program to assist in treatment recommendations since 2011 [24]. Preemptive testing refers to pharmacogenetic testing done prior to the initiation of therapy rather than in response to failed treatment (e.g., reactive testing). These results are then uploaded into the electronic health record (EHR) and remain with the patient chart for future use [29]. Other thriving pharmacogenetic testing programs include Vanderbilt University Medical Center's Center for Precision Medicine (Nashville, TN) and the pharmacogenetics implementation program at the University of Chicago (Chicago, IL) [30]. Several large health systems have also developed robust pharmacogenetic testing programs including Medstar Health (Columbia, MD), Geisinger Health (Danville, PA), and Northshore University HealthSystem (Evanston, IL). Northshore University Health System provides pharmacogenomic consultations via their MedClueRx program, analyzes patient pharmacogenetic data on site, and transfers information to their Pharmacogenomics Clinic, where the healthcare team determines recommended treatment based on pharmacogenetic results [31]. Finally, the Implementing Genomics in Practice (IGNITE) program funded by the National Institutes of Health works to improve integration of genomic health information into clinical EHRs and clinical decision support systems with a goal to ensure genetic data is properly used in therapeutic treatment [32].

The expansion of precision health, and pharmacogenetic testing implementation is exciting and promising, however, these programs have one thing in common: they are located in large, urban areas. Patients living in rural communities are left with limited access to pharmacogenetic testing services. There are a small number of community-based initiatives implementing pharmacogenetic testing programs. Imagenetics at

Sanford Health has received a hundred million dollar gift to expand access to pharmacogenetic testing across North and South Dakota, states with a high proportion of rural residents [33]. This program has emphasized providing pharmacogenetic education to providers and patients while offering testing at little to no cost. A new initiative in Montana, one of the most rural locations in the country, hopes to use telehealth technologies to expand pharmacogenetic testing implementation in rural and underserved areas. The Skaggs Institute for Health Innovation (SIHI) located within the Skaggs School of Pharmacy at the University of Montana is exploring strategies to implement pharmacogenetic testing through telehealth technologies to ensure equitability [34]. My research thesis is an extension of the work conducting in SIHI. Although a handful of localized implementation efforts exist in the US, health innovations such as pharmacogenetics continue to remain inaccessible for some of groups due to inequitable distribution.

1.5 Equitable Access to Pharmacogenetic Testing

Access to new healthcare technologies is often out of reach for rural, underserved and minority groups due to inequitable distribution. Pharmacogenetic testing implementation is expanding across the US in urban settings, however, rural, community-based health systems are often left behind when initiating pharmacogenetics programs. Geographic remoteness, a lack of pharmacogenetic expertise, and EHR integration issues are commonly described implementation barriers that are further exacerbated in rural and underserved communities [35] Access to pharmacogenetic expertise in rural health systems is rare. Pharmacogenetic testing can be outsourced to large testing companies, however, providers in community-based health systems commonly do not have training to interpret and implement pharmacogenetic test results into patient treatment plans.

Additionally, clinical decision support programs for pharmacogenetic testing are not typically available in rural health systems. Providers typically do not have the option to integrate pharmacogenetic test results into their EHR where it can be readily available, leaving out pharmacogenetic information for future treatment. Test results are unusable with limited pharmacogenetic expertise and unattainable clinical decision support tools. Therefore, clinicians need to refer their patients to specialists in larger, urban areas with pharmacogenetic experts on staff, resulting in increased financial burden on patients who may need to travel long distances to reach specialty care. Novel implementation strategies need to be explored and developed to properly implement pharmacogenetic testing into rural healthcare settings.

Furthermore, engaging diverse populations in genomic research is crucial for obtaining comprehensive knowledge of variation in the human genome. Yet genomic research, including pharmacogenetics, has primarily included participants of European ancestry. The All of Us initiative has a goal to recruit 1 million US participants and to create a large and diverse biomedical research repository. Researchers have attempted to conduct targeted recruitment efforts across the country to enroll individuals across multiple regions, racial and ethnic groups, ages, genders, disabilities, and socioeconomic backgrounds. This effort, which began in 2018, has only recruited 100,000 participants as of March 2022, and researchers have struggled to ensure underserved and minority populations are included. There are several enterprises alongside All of Us attempting to include as many participants as possible including the Million Veterans Program and the UK BioBank, and Iceland's Decode Genetics initiative [36-38]. These precision medicine and genomic research programs are meant to be utilized by genetic researchers in the development of precision medicine technologies, and therefore, must have greater diversity to be of value for a broader group of people.

These worldwide efforts have aimed at increasing diversity of genomic research participants—with the largest increases in populations of Asian ancestry—participants with African, Hispanic, Indigenous, Middle Eastern, and Oceanian ancestry remain troublingly underrepresented [39, 40]. This bias is problematic because the prevalence and frequency of variants in pharmacogenes is highly variable across global populations [41, 42]. The consequences of this lack of diversity in pharmacogenetic data means the variants that are best understood are those frequently found in European populations, while collective knowledge of common and important variants in non-European populations is far more limited. Groups such as CPIC rely on published data to make their dosing recommendations for specific genetic variants, but variants that are underrepresented in published pharmacogenetic studies may not be sufficiently characterized to reliably predict how they affect drug response. As a result, these variants may not receive a recommendation in the guidelines, causing biases in the underlying research studies to persist through dosing recommendations and clinical utility.

It is clearly documented that innovations in healthcare are inequitably disseminated from urban academic medical centers to rural, underserved clinics that treat marginalized patients. The growing field of pharmacogenetics is no exception to this pattern of distribution. Researchers must continue to construct unique approaches to equitable healthcare delivery. For example, American Indian and Alaskan Native (AIAN) populations have largely been left out of pharmacogenetic research. This is due, in part, to historical trauma AIAN peoples experienced in prior genetic research projects, in addition to the contemporary injustices these communities face with improper healthcare innovation diffusion [43-46]. Researchers must conduct ethical pharmacogenetic

research in a way that is not only culturally sensitive to this history, but also focuses on research dissemination and equitable access to technologies arising from research in future efforts. Much is unknown about the genetic variability in tribal populations, and it is possible pharmacogenetic testing platforms generated from research in European descendent populations may not be applicable to tribal patients.

1.6 Telehealth as a Tool for Broader Access to Specialty Care

Telehealth, also referred to as telemedicine, is healthcare delivery via a technological or web based interface. Technologies in telehealth have grown exponentially in the past decade with advancements in video conferencing software and internet broadband capabilities [47]. Telehealth models first gained traction with rural and primary care providers, who found benefit in receiving telehealth consultations from specialists (doctor-to-doctor) in lieu of sending patients to specialty care services, which could mean traveling long distances. The market has since grown to include patient-to-doctor telehealth visits. Although some argue particular nuances and patient care measures cannot be assessed through a video screen, telehealth visits have gained popularity among patients living in rural locations. Telehealth has especially garnered interest among mental healthcare professionals and patients, because psychiatric assessment questionnaires, such as the patient health questionnaires, can easily be delivered remotely [48, 49]. In qualitative studies gauging success of rapid telehealth implementation due to the consequences of the COVID-19 pandemic, young mental health patients and psychiatric providers expressed positive perspectives regarding the use of telehealth in healthcare delivery [50, 51]. Prior to 2020, there were several restrictions regulating telehealth services. Insurance policies did not typically cover the cost of telehealth visits. If coverage was available, there were specific rules providers

needed to follow when conducting visits. Providers who offered telehealth care needed to practice in a traditional clinic, and they were required to hold an established relationship with their patients. The COVID-19 pandemic accelerated changes in legislature and insurance policy as a means to ensure social distancing and protect public health.

Laws passed in Montana in early 2021 removed several site restrictions on telehealth service providers. This offered clinicians the opportunity to conduct telehealth visits from home rather than in a clinic or office, removed the statute requiring patients and providers to have an established relationship before conducting virtual care, and required insurance companies to cover appointments conducted via telehealth modalities. These laws were initially planned to be temporary, however, they became permanent later that year [52]. Telehealth policy advancements opened the door for patients to access specialty care at an unprecedented rate. Additionally, under the new insurance regulations, services are no longer limited to affluent patient populations who can afford out-of-pocket costs. Underserved communities—particularly those living in rural areas or of lower socioeconomic status—now have resources to access new health initiatives. If implemented correctly, this model could serve as a novel strategy to begin pharmacogenetic testing programs for these communities.

1.7 Pharmacogenetic Testing Implementation in Montana

Pharmacogenetic testing is a tool used by providers and researchers to guide prescribing decisions based on patient-specific results. CPIC provides clinical guidelines for many drug-gene pairs across therapeutic areas including cancer, mental health, pain management, and cardiovascular disease treatment. Testing assists providers by

providing information on patient specific pharmacokinetics and pharmacodynamics. Guidelines offer treatment recommendations for dose or medication selection based on patient specific phenotypes. Pharmacogenetics testing prior to medication initiation can prevent potential side effects and ensure proper therapeutic dosing. Advanced technologies such as pharmacogenetics testing, however, have not been equitably utilized across US populations. Testing has been implemented and utilized in large academic medical centers with extensive resources and large patient populations, yet it has rarely been implemented in rural regions due to inaccessibility of information, lack of resources for providers and patients, and a shortage of healthcare providers in rural areas. Additionally, underserved patients living in rural areas, including AIAN people and those with disadvantaged socioeconomic situations, lack access to innovative and potentially treatment-altering technologies.

With this in mind, the overall goal of my thesis is to generate knowledge that facilitates pharmacogenetics testing implementation in facilities that service underserved and rural areas by assessing the challenges unique to these communities, especially in Montana. My general hypothesis is that understanding barriers and facilitators for pharmacogenetics implementation in rural and underserved health systems will increase the likelihood of successful implementation and accessibility to this technology for underserved communities.

The Woodahl lab has a long-standing research partnership spanning almost 15 years with the Confederated Salish and Kootenai Tribes (CSKT) on the Flathead Reservation [35, 44, 53-55]. This community-academic partnership is among the first to engage an AIAN community in precision medicine and pharmacogenetic research. We remain one of the few groups engaging rural and tribal populations in pharmacogenetic research and

implementation. We have established partnerships with 3 healthcare centers in Montana: CSKT Tribal Health Department (CSKT) in St. Ignatius, MT; Partnership Health Center (PHC) in Missoula, MT; and Shodair Children's Hospital (Shodair) in Helena, MT (Table 2.1). We assessed multiple facilities to ensure a mixture of different underserved communities to achieve our goal of equitable access to pharmacogenetic testing sources. We have completed needs assessment interviews at all 3 sites, and my goal is to utilize these results to expand on the work in the Woodahl lab.

My research involves two main projects: 1) a needs assessment study with providers and healthcare personnel at CSKT, PHC, and Shodair; and 2) an in-depth analysis to beginning planning for pharmacogenetic testing implementation at Shodair.

Specific Aim 1: Conduct a needs assessment to evaluate readiness and feasibility for pharmacogenetic testing implementation. *Hypothesis: Interviewing key stakeholders serving rural and underserved communities will provide insight into the unique barriers and facilitators faced when implementing pharmacogenetic testing.*

Specific Aim 2: Plan for implementation of pharmacogenetic testing at Shodair Children's Hospital based on results from the needs assessment. *Hypothesis: Results from Specific Aim 1 will serve as a framework for developing a plan for pharmacogenetic testing implementation, of which Shodair is the ideal location to pilot the project.*

I hypothesize that including key stakeholders in the evaluation of barriers and facilitators to pharmacogenetic implementation in rural and underserved communities will help identify challenges and obstacles to implementation in unique facilities within Montana

and provide novel strategies for implementation. The overall goal of my thesis is to generate knowledge that advances pharmacogenetic implementation practices in underserved areas, including rural and tribal populations in Montana. Additionally, I aim to generate a framework for pharmacogenetic testing implementation using telehealth technologies that can improve accesses to testing in these locations and provide novel strategies for underserved and rural communities in the US.

The novelty of this research is the inclusion of rural, underserved, and tribal communities in pharmacogenetic implementation research. We have committed to conducting research that engages the CSKT community and disseminate research findings directly to CSKT clinicians, participants, and tribal leadership in order for the research to benefit the community. Additionally, our partnership with PHC and Shodair will advance pharmacogenetic implementation in healthcare settings that serve rural patients.
My research has assessed the barriers that stall implementation and facilitators that launch new technological programs for underserved populations and the facilities that care for them in pharmacogenetic implementation research. The next two chapters will outline results of these efforts. Our goal is to ensure equitable access to pharmacogenetic testing for all populations regardless of geographic location, socioeconomic status, or tribal affiliation.

Figure 1.1. Pre-emptive pharmacogenetic testing for citalopram

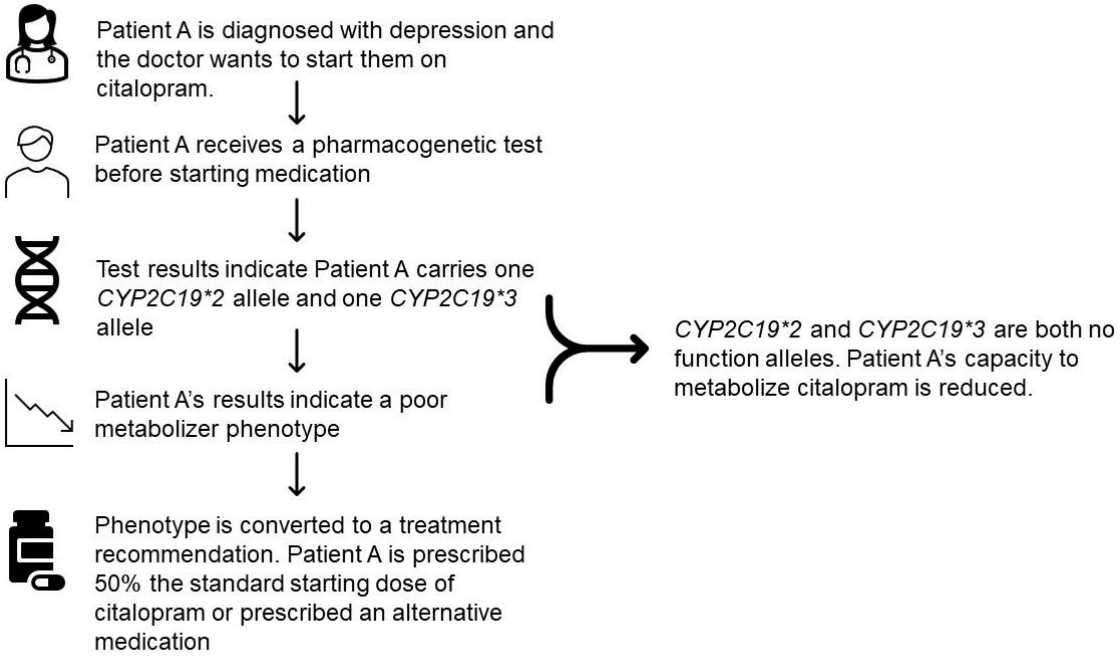

Table 1.1. Examples of CPIC clinically-actionable gene-drug pairs

Disease state category	Medication	Relative Pharmacogenes
Cardiology	Clopidogrel	*CYP2C19* [56-58]
	Warfarin	*CYP2C9, CYP4F2, VKORC1* [59, 60]
Gastroenterology	Omeprazole	*CYP2C19* [61]
	Ondansetron	*CYP2D6* [62]
Infectious Disease	Abacavir	*HLA-B* [63, 64]
	Voriconazole	*CYP2C19* [65]
Neurology	Oxcarbazepine	*HLA-B* [23]
	Phenytoin	*HLA-B, CYP2C9* [20, 21]
Oncology	Fluorouracil	*DPYD* [66]
	Thiopurines	*TPMT* [67]
	Tamoxifen	*CYP2D6* [68]
Pain management	NSAIDs	*CYP2C9* [69]
	Opioids	*CYP2D6* [70]
Psychiatry	TCAs	*CYP2C19* [71]
	SSRIs	*CYP2D6, CYP2C19* [15]
	Atomoxetine	*CYP2D6* [72]
Other	Statins	*SLCO1B1* [73]

Chapter 2. Ensuring Equity: An Evaluation of Challenges and Facilitators for Pharmacogenetic Implementation in Rural and Tribal Communities

2.1 Introduction

Growing evidence supports the use of pharmacogenetic-guided medication management, yet adoption into standard practice has thus far been primarily limited to academic medical centers and large health systems serving urban patients [74]. Consistent with the diffusion of innovations theory, which postulates that extended periods of time are required for new health innovations to be widely disseminated, patients receiving care in rural primary care settings are often last to receive new treatments, care strategies, and the benefits of new health services [75]. Examples of this variable diffusion—or failure to integrate innovations into health systems serving neglected populations—have been observed for a variety of modern medical technologies, from advancements in clinical imaging, to evidence-based changes in clinical protocols, and to the uptake of telehealth delivery systems [76-80]. Efforts to broadly democratize pharmacogenetic testing have faced barriers, with limited examples of pharmacogenetic testing implementation in rural and tribal healthcare settings [81-84].

Unique challenges impact access to healthcare services in rural, underserved, and resource-limited communities. Examples include cultural or financial barriers to care, underdeveloped public transportation, and inadequate broadband internet access that hinder the implementation of telehealth strategies [80, 85]. Additionally, despite ongoing federal and state efforts to incentivize professionals to serve rural areas, such communities face an ongoing shortage of physicians and trained health professionals and a scarcity of specialty care [86]. The most recent data provided by the federal Health Professional Shortage Area (HPSA) Dashboard reports that approximately 65% of the 7,828 HPSA-designated areas for primary care in the United States met criteria for rural status, with 19% receiving HPSA status based on a shortage of providers within a

county or group of neighboring counties in remote geographic areas [87]. An estimated 30 million people utilize federally qualified health centers (FQHCs) for care including 1 in 5 rural residents and 1 in 3 persons living in poverty [86]. While medically underserved designations have helped to establish and maintain health services for groups frequently facing barriers to healthcare, disparities have continued to permeate health systems and access to specialty services remains an ongoing challenge for these groups [88].

Aside from the barriers faced by patients living in poverty or in geographically isolated locations, some Americans continue to experience significant health disparities in relation to race and ethnicity. As highlighted by the COVID-19 pandemic, specific racial and ethnic groups experience disproportionately high rates of severe COVID-19 illness, particularly African American, Hispanic Americans, and American Indian and Alaska Native (AIAN) people, further emphasizing longstanding health disparities [89]. This trend is true for many conditions, with AIAN peoples continuing to face disproportionate disease burden for several chronic illnesses including diabetes, liver disease, and respiratory diseases, and have lower overall life expectancy rates than the general population [88, 90].

Recent studies have demonstrated that healthcare providers anticipate an increase in the use of pharmacogenetics-guided prescribing in the near future [91-94]. Even so, many still consider pharmacogenetic testing a “luxury” service rather than a critical clinical decision-making tool. In urban settings, fiscal barriers tend to delay implementation and these concerns are only amplified in rural settings [95, 96]. Additionally, a well-documented shortage of genetic specialists in the United States demonstrates ongoing demand for professionals with training to deliver and interpret genetics-related services [97-99]. Given the challenges that many underserved

communities face, the potential of pharmacogenetic testing to optimize medication therapy in a timely manner is compelling. Their exclusion from pharmacogenetic research and implementation efforts may exacerbate healthcare disparities. Additionally, pharmacogenetic research has largely included participants primarily of European ancestry, with knowledge of pharmacogenetic variation in diverse populations desperately lagging [100-102].

To overcome the unique barriers to implementation in rural and tribal settings, it is imperative that creative solutions are developed to ensure pharmacogenetic testing is integrated into practice for all patients. Our goal is to inform the development of a pharmacogenetic implementation strategy based at University of Montana (UM) focused on serving neglected patient populations, and subsequently, to inform implementation in rural areas. Montana is populated by diverse, underserved patient groups, including rural and tribal populations, patients of lower socioeconomic status, and patients with limited access to care in sparsely populated rural regions [103-106]. Montana—the fourth largest state in the United States—at approximately 147,000 square miles, boasts a population density of just 6.8 persons per square mile with two of every three residents living in rural areas [104]. In total, 55 of 56 counties in Montana have received some form of HPSA designation [87]. Montana is also home to 12 Tribal nations and AIAN peoples are the largest minority group in the state making up almost 7% of the population [106, 107].

We have engaged three partner sites in Montana focused on providing patient-centered care to historically neglected populations. The Tribal Health Department of the Confederated Salish and Kootenai Tribes (CSKT)—with whom we have a long-standing community-academic research partnership in pharmacogenetics [108-110]—provides a

network of primary care health and wellness services to patients with Indigenous ancestry throughout the Flathead Reservation in Montana [111]. Partnership Health Center (PHC)—a FQHC in Missoula, Montana—provides a variety of healthcare services and seeks to provide equitable, comprehensive care for insured or uninsured patients of all income levels [112]. Shodair Children's Hospital (Shodair) in Helena, Montana serves children and adolescents throughout the state providing acute, residential, and outpatient psychiatric care [113]. With our partners, we seek to integrate pharmacogenetic testing services across a broad range of therapeutic applications utilizing telehealth to overcome obstacles of geographic remoteness.

Our study aims to identify unique facilitators and barriers to pharmacogenetic implementation among disadvantaged, underrepresented, and neglected populations. The data collected through semi-structured interviews will inform a needs assessment for future implementation efforts, specifically tailored to improve access to pharmacogenetics among patient populations experiencing significant health disparities. Our goal is to also evaluate stakeholders' perceptions of using an innovative telehealth model to deliver pharmacogenetic consultations statewide. We expect that the provision of a centralized resource operating via a "hub and spoke" model may expand access to pharmacogenetics for rural, underserved, and tribal patients, creating equitable frameworks for delivery in other resource-limited health systems.

2.2 Materials and Methods

2.2.1 Study Setting

We completed interviews with healthcare professionals, administrative staff, and informatics professionals at three different sites (CSKT, PHC, and Shodair) serving underserved and neglected populations in Montana (Table 2.1). Each partner site offers a mixture of primary care and specialized treatment and seeks to provide ethical and equitable care for patient populations experiencing health disparities. This work was approved by UM and Salish Kootenai College Institutional Review Boards.

2.2.2 Study Design, Data Collection, and Analysis

We conducted interviews to elicit stakeholders' perceptions, attitudes, and opinions regarding pharmacogenetic implementation in rural settings—as well as potential impacts on patients and populations served—at CSKT, PHC, and Shodair. Partners at each site helped identify prospective participants, which generated referral sampling within each location. For interviews conducted at PHC and Shodair, we developed a semi-structured interview guide utilizing components of the Consolidated Framework for Implementation Research (CFIR) [114]. Participants were asked to complete a brief survey to collect demographic information and general perceptions of pharmacogenetics and implementation strategies via Qualtrics (Provo, UT, Unites States). Interviews lasted 30-60 minutes and were conducted in person or via telephone by members of the research group from August to October 2019. For interviews conducted at the CSKT Tribal Health Department, we conducted a secondary analysis of data from a prior formative study concerning provider perceptions of precision medicine, of which pharmacogenetics is a component. Interviews were semi-structured, lasted 30-60 minutes, and were conducted over the telephone by a member of the research group in April 2019. Because the CSKT interviews did not collect participant views regarding telehealth for pharmacogenetic consultation, those results are not reported the CSKT

cohort. Interviews at all sites were halted when theoretical saturation was achieved [115].

Interviews were audio-recorded and transcribed for a descriptive thematic analysis to identify major themes generated from participants' knowledge, attitudes, and beliefs [116]. Interview transcripts were uploaded into ATLAS.ti (Berlin, Germany). The study team worked together to iteratively develop a codebook. The resulting codes and themes were independently evaluated by the full research team and were subsequently analyzed for any remaining discrepancies or sources of potential bias. The codebook was finalized and applied it to the full dataset with the team meeting to resolve differences as needed.

2.3 Results

2.3.1 Overview

Across the three sites, 48 participants were recruited and interviewed (Table 2.2). Interviews sought to include participants with a variety of clinical, administrative, and technical expertise as implementing new interventions affects not clinical workflow, but also workflow other healthcare staff and administrators. Major themes are highlighted below with sections beginning with a summary of findings that were common across sites followed by findings unique to each. Direct quotations provide evidence for each major theme (Tables 2.3-2.6).

2.3.2 Opportunities to mitigate medication management concerns unique to neglected populations

Participants across sites shared concerns regarding polypharmacy and the potential financial burden of medication therapies for their patients (Table 2.3). They cited goals of simplifying medication management for their patients on more complex regimens and limiting potential drug interactions. Additionally, participants described the importance of maximizing medication therapies in a time-sensitive manner as a primary treatment goal, highlighting their concern for the lack of access to adequate follow-up care that their patients often face. For these underserved populations, a breadth of health inequities presents difficulties in medication management and the vast distances between sparsely populated communities in Montana further complicates appropriate follow-up.

In addition to challenges in medication management for patients in rural communities, participants who serve Tribal patients noted specific barriers. As a health system focused on providing care grounded in tribal values for any and all members of federally recognized tribes, CSKT Tribal Health providers were concerned that the clinical implementation of new medication therapies or treatment strategies in rural practice settings is often delayed, which negatively impacts tribal communities. Several participants described this phenomenon as a challenge in their everyday practice. CSKT participants noted that when new innovations are made available, they are seldom trialed adequately in all populations. For example, some providers expressed concerns that treatment options for many chronic conditions lack evidence to support their use in non-European descended populations. Participants opined that many aspects of modern medicine and its practice fail to adequately address a variety of clinically important factors, including a host of environmental or genetic factors, as well as historical and present barriers to accessing care for tribal patients.

Participants at PHC serve patients who experience inequitable access to healthcare and a variety of barriers to medication management. PHC participants heavily consider barriers their patients face—including poverty, homelessness, and being members of minoritized or marginalized groups—when developing treatment plans. Medication therapies and strategies are adjusted to help address specific concerns such as cost, monitoring, and access. As the patients treated at PHC may have a variety of the aforementioned financial, environmental, or social factors influencing their care and treatment plans, optimizing medication therapies and reducing barriers to access or improving medication therapy outcomes were primary concerns for healthcare professionals.

Participants at Shodair primarily serve another one of Montana's most vulnerable populations, children and adolescents undergoing psychiatric treatment, as well as serving as the primary hub for medical genetics resources and services throughout the entire state of Montana. Participants spoke about the difficulty of managing pediatric patients on a variety of psychiatric medications, who often undergo multiple medication changes—a process that can take months to years—until they reach therapeutic stability. Many patients at Shodair are initially admitted to the acute inpatient unit and subsequently transitioned to outpatient care following adequate symptom management. Providers described concerns regarding the timeliness of achieving therapeutic drug plasma levels and subsequent desired response; many psychiatric medications require trial periods of 2-4 weeks before symptom improvement, yet the typical acute inpatient stay is 7-10 days, making initial treatment selection especially critical. Additionally, providers cited challenges in successfully transitioning patients from the hospital setting back to community-based care located elsewhere in Montana, considering many patients return to rural or tribal communities with limited access to specialty psychiatric

care. Providers stated that due to the shortage of psychiatric resources and care options for pediatric patients in geographically isolated communities throughout Montana, changes to medications or treatment strategies initiated at Shodair are not always effectively continued or monitored following discharge.

2.3.3 Potential barriers to pharmacogenetic implementation for underrepresented populations

Across all sites, interviewees touched on the expected concerns surrounding the cost of pharmacogenetic testing services, reimbursement for the tests and consultations of results, education and buy-in for providers unfamiliar with pharmacogenetics, and anticipated challenges with the integration of results into the electronic health record (EHR) to assist with clinical decision support (Table 2.4). Based on the unique make-up of the patient populations served, specific barriers to successful implementation became central within interviews amongst each respective site.

Providers at CSKT Tribal Health reported their patients may have mistrust in genetics, including pharmacogenetic testing and research, given historical misuse and abuse of genetic data from AIAN peoples. In the context of experiences with data stewardship in genetics research, participants noted that the majority of research completed to date has failed to adequately address concerns within AIAN populations regarding discrimination, stigma, and other potential harms. Some providers considered that existing evidence may not be applicable to AIAN populations due to the lack of ancestral diversity in research used to generate pharmacogenetic testing arrays and testing guidelines.

Interviewees at PHC identified cost of healthcare services as the primary barrier to their patients. Many participants described concerns regarding the prioritization of testing among those patient already facing a variety of sociodemographic factors that impact access to care and how to determine which patients could benefit most from the added expense of pharmacogenetic testing. Concerns around healthcare equity were a strong theme at PHC and providers speculated on how to ensure that testing was an option for all patients, not only those who could afford it. Several participants anticipated that there may be hesitancy from practitioners who believe the return on investment from pharmacogenetic testing remains inadequate, particularly within a resource-limited practice setting. Sociodemographic challenges already limit access to basic preventative health or primary care services for many PHC patients. Resource constraints lead to hesitancy toward health innovations that are not yet accepted as standard of care among PHC providers. The risk of overburdening providers with more information or further complicating workflow was apparent among participants.

Shodair participants identified the turnaround time for testing results to be made available to practitioners as a critical concern. Many felt that delays in receiving results would limit the value of pharmacogenetic testing in the acute, inpatient setting and that testing may have greater utility in the outpatient setting. Participants also identified the successful integration of pharmacogenetic testing results in the EHR as a key factor in achieving provider buy-in and perceived utility. Participants said that Shodair currently lacks a location or protocol for the standardized storage of pharmacogenetic testing results. Participants emphasized the need to ensure security in inter-facility data transfers, particularly for genetic information. There were concerns that even if the testing were utilized, many providers—especially those without specialized training in

pharmacogenetics—would not feel comfortable interpreting results themselves and using them to guide prescribing decisions.

2.3.4 Facilitators and perceived value of pharmacogenetic testing services targeted to underserved patient populations

Many individuals interviewed shared positive perceptions of the ability of pharmacogenetic testing services to help achieve therapeutic benefit and reduce time to effective dose (Table 2.5). Participants across all sites identified additional training, education, and resources for staff as a significant facilitator to implementation. Perceived benefits that were noted across all sites included reduced risk for adverse drug events related to patient phenotype status, and improved medication management outcomes for patients with limited access to follow-up services due to social, environmental, or financial barriers.

A primary facilitator of an implementation effort highlighted at CSKT Tribal Health was the long-standing partnership and engagement fostered between the CSKT and UM researchers, built on more than a decade of ongoing pharmacogenetic research. Healthcare stakeholders interviewed at CSKT shared positive perceptions regarding the clinical utility of pharmacogenetic testing. Practitioners and health professionals generally agreed pharmacogenetic testing could support individualized, targeted treatment for their patients and could be utilized to minimize or reduce preventable adverse reactions related to medications. Several participants described potential benefits in helping to minimize risks of polypharmacy as a result of more targeted dosing strategies.

Participants at PHC prioritized achieving provider buy-in and ensuring that providers have sufficient education, training, and point-of-care resources. Participants suggested that identifying pharmacogenetics “champions” within the organization would serve as a key facilitator of successful implementation. Several participants pointed to established PHC protocols for initiating new clinical services and emphasized the importance of engagement with all departments. New programs at PHC are generally piloted in a smaller area of the clinic, where major barriers and concerns can be addressed quickly and without impact on the entire clinic workflow. Programs that perform well in the pilot are then expanded to other departments. PHC participants prioritized educational opportunities for staff members as key to successful implementation. Several participants recommended that education—including presentations from experts in the field and connecting with practitioners as “point-of-contact” resources—would facilitate pharmacogenetic testing.

Shodair participants emphasized the importance of effective integration of pharmacogenetic testing results into the EHR and clear channels of communication between Shodair and the UM pharmacogenetic consultation service exhibiting secure and protected data sharing. Providers at Shodair prioritized an approach that would expedite the timeline to effective medication management and more targeted therapy, which they believed could generate better post-discharge outcomes for patients, including reduced rates of readmission. Participants felt that an implementation effort in an outpatient setting would provide better opportunities for reimbursement and more flexibility in turnaround time of testing results.

2.3.5 Role of a unique telehealth delivery model for pharmacogenetic consultations

During interviews, a telehealth delivery model offered by pharmacogenetic experts based at UM was introduced as a means to achieve equitable pharmacogenetic testing implementation (Table 2.6). As described above, participants at PHC and Shodair were questioned on their opinions of utilizing telehealth technology to provide pharmacogenetic consultations on test results and education to providers on the use of pharmacogenetics. These questions were not addressed within interviews completed with CSKT participants as the results from the CSKT were from a secondary analysis of data from a previous study that did not address telehealth. Participants expressed positive perceptions of using telehealth for the return of pharmacogenetic results and valued a service that could connect providers to resources and expertise without requiring significant changes to provider education and workflow on-site. Participants preferred that testing results be integrated into the EHR and providers receive both result interpretations and treatment recommendations. Providers also discussed the importance of having pharmacogenetic experts available for future clinical support and education, as pharmacogenetics-driven prescribing guidance continues to evolve. Participants spoke of the potential benefits of increasing access to specialized pharmacogenetic testing for populations who would otherwise have to travel extensive distances to access this expertise.

Participants at PHC identified the importance of having a centralized resource for pharmacogenetic recommendations, guidance, and support as a major benefit for this site, as well as other health systems providing primary care or behavioral health services across the state. Tasked with providing a great variety of primary care services, providers reported that integration of a new service like pharmacogenetic testing—with applicability across a range of specialties—would not be feasible for general primary clinicians to manage independently without a tailored support system. The integration of

a consultation service provided via a centralized resource was particularly attractive to PHC clinicians and several interviewees highlighted the importance of improving access to pharmacogenetic resources for individuals of all backgrounds. Participants shared positive perceptions regarding telehealth modalities for limiting costs while increasing access to these services for a variety of patient populations.

Participants at Shodair felt a telehealth model would serve as an appropriate strategy for successful integration of pharmacogenetic testing into outpatient services. Participants noted that additional, dedicated resources and personnel would be required to provide a pharmacogenetic testing service to Shodair providers and their patients. Therefore, interviewees identified a telehealth model as a potential alternative to provide patient-specific recommendations, guidance, resources, and ongoing education to providers. Participants felt that providing a pharmacogenetic service—not only to the providers located at Shodair, but also as a resource for providers across the state—could help to ensure the testing results are utilized well after patients are discharged.

2.4 Discussion

Innovative clinical services—like pharmacogenetics—are often considered out of reach for patients in rural and tribal areas due to concerns regarding the sustainability and financial feasibility of new programs, perpetuating a troubling trend in which novel healthcare advances remain largely inaccessible for patient populations already experiencing significant health disparities. By failing to seek out unique solutions for pharmacogenetic implementation strategies in rural and tribal settings, existing health disparities may be exacerbated. For patient populations with limited access to care, high-quality medication management, access to pharmacogenetic testing, and

appropriate follow-up are significant concerns among providers. Through qualitative interviews conducted with three early-adopter sites throughout the state of Montana, we found an interest in the use of pharmacogenetic testing to help address these concerns. These interviews demonstrated that facilities serving rural and tribal patients are uniquely situated to benefit from pharmacogenetic testing and consultation delivered remotely via telehealth. Given well-established obstacles for geographically isolated and underserved communities, telehealth offers the ability to provide specialized and innovative clinical services to patients who may stand to benefit from targeted treatment strategies most.

At the CSKT Tribal Health Department—a health system providing care for those individuals of tribal ancestry—participants shared concerns regarding patient engagement and acceptance of pharmacogenetic testing given historical misuse and abuse of genetic data among Indigenous peoples. Within this context, providers and administrators at this site emphasized the importance of educational resources regarding pharmacogenetic testing for both healthcare providers and patients, providing special consideration and sensitivity for AIAN patient populations. Participants shared concerns that existing guidelines and research within the pharmacogenetics field have failed to adequately include Indigenous peoples and expressed a desire to continue fostering relationships of mutual trust between the CSKT Tribal Health, the patients they serve, and ongoing pharmacogenetic research initiatives with the research team at UM.

At Partnership Health Center—a community health center that serves patients across the sociodemographic spectrum—participants' concerns centered on the importance of developing a strategy for equitable implementation of pharmacogenetic testing. Participants identified equitable opportunity, in terms of both cost and physical access to

education and counseling resources, as a primary barrier to widespread adoption. Additionally, as a site that offers comprehensive primary care services addressing a multitude of disease states, PHC participants highlighted concerns surrounding the shortage of specialized expertise regarding pharmacogenetic testing and lack of access to consultation services for primary care providers and patients in rural areas. Participants were enthusiastic for readily available resources and support through a UM-based centralized pharmacogenetic service and described it as a critical component of a successful implementation strategy.

As a site that serves as a leader and statewide resource for pediatric psychiatric services, providers at Shodair Children's Hospital were familiar with both barriers and key facilitators of implementing pharmacogenetic testing services within their practice setting. Interviewees identified outpatient settings—in comparison to inpatient or acute care—as the ideal point for pharmacogenetic testing implementation and integration within existing workflows. Participants prioritized potential benefits of partnering with UM to provide pharmacogenetic consultations to advance the delivery of cutting-edge medication management initiatives to patients throughout the state. Participants at Shodair also valued a successful integration of pharmacogenetic test results into the EHR as an imperative step for therapy modifications and follow-up, particularly for patients transitioning from Shodair to their local community care settings.

In addition to these novel findings in rural, underserved, and tribal healthcare settings, participants also expressed themes that have been described in previous analyses of health professionals' perceptions of pharmacogenetic testing and implementation feasibility [81, 84, 92-94, 117]. Common themes among all three sites included concerns regarding adequate turnaround time for testing results, concerns around cost and

reimbursement of testing, and goals for successful integration of testing results into an EHR. Participants were generally positive regarding a pharmacogenetic implementation effort and considered decreased time to effective dose, minimizing the trial-and-error process of prescribing, and reducing adverse drug events as potential benefits. Participants at all sites valued pharmacogenetic testing results as a clinical decision support tool, but expressed concerns that the utility of the results may not be fully realized without significant education or clear guidance from experts in the field. Overall, participants involved in the analyses shared positive perceptions of a UM-based consultation service providing clinical recommendations and serving as a local resource for pharmacogenetic expertise.

Participants were enthusiastic that leveraging telehealth modalities could aid in pharmacogenetic implementation across a geographically expansive region and provide critical access to expertise otherwise unavailable to patients in rural and underserved areas. Telehealth has been proposed as a strategy to increase access to specialized services for rural communities and may be a valuable tool for pharmacogenetic implementation [118, 119]. The COVID-19 pandemic has highlighted opportunities for telehealth to address healthcare disparities, however, the adoption is still lower in nonmetropolitan areas [120, 121]. Access to high-speed internet is also a challenge for rural communities to take full advantage of the benefits offers by telehealth, although Montana is forward-thinking in improving and expanding high-speed internet for its citizens. In December 2020, the Federal Communications Commission awarded $125 million to Montanans firms to develop broadband infrastructure in rural regions as well as a providing internet licenses to the 7 Tribal Reservations through the Rural Tribal Priority Window Initiative [122, 123]; and in February 2021, the Montana State Legislature unanimously voted to expand telehealth coverage requirements and remove site

restrictions for services in response to rising trends in telehealth due to the COVID-19 pandemic [124]. These expansions demonstrate significant interest in utilizing telehealth to improve access to health services for Montanans and bodes well for our strategy to develop integrated pharmacogenetic telehealth solutions for stakeholders in rural, underserved, and tribal areas.

Our findings will inform an implementation strategy focused on improving access to pharmacogenetics for underserved and neglected patient populations, and increasing inclusion of underrepresented groups in pharmacogenetic research. Given well-established challenges to improving access to even baseline preventative health services in some rural, underserved, and tribal communities (e.g., low provider numbers, significant travel distances, and limited incomes), achieving equal access to care—especially for costly specialty services like pharmacogenetic testing—remains challenging. Through the development of a centralized “hub and spoke” pharmacogenetic consultation service at UM, we will continue to explore critical challenges and facilitators for implementation strategies focused on serving underserved communities and the clinicians caring for them. By leveraging telehealth modalities for the dissemination and implementation of pharmacogenetics to underserved areas, our work may generate solutions that have wider utility and applicability for improving access to pharmacogenetic testing for patients living in a variety of resources-limited settings throughout the United States. We will pursue a pharmacogenetic implementation effort in an ethical and equitable manner through the development of a model focused on improving diffusion of pharmacogenetics to communities that have historically been the last to benefit from cutting-edge health innovations.

Table 2.1. Partner Site Descriptions

	Confederated Salish and Kootenai Tribes (CSKT)	Partnership Health Center (PHC)	Shodair Children's Hospital (Shodair)
General Descriptor:	A network of healthcare clinics serving the CSKT based out of St. Ignatius, Montana.	A federally-funded community health center located in Missoula, Montana.	A pediatric psychiatric hospital located in Helena, Montana, also providing the state's only comprehensive medical genetics services including diagnostic evaluation, care coordination, and risk assessment.
Services Offered:	• Medical • Dental • Pharmacy • Behavioral health • Telehealth services • Physical therapy • Optical • Audiology & Speech • Community Health	• Medical • Dental • Pharmacy • Behavioral health • Telehealth services	• Acute and residential psychiatric services • Outpatient psychiatric care • Medical genetics services (on-site and remote) • CLIA certified diagnostic genetics laboratory • Telehealth services
Primary Patient Populations:	Tribal Health Clinics focus on providing high-quality care to recipients "grounded in Tribal values" for the CSKT • 11,000 eligible recipients which includes CSKT members and descendants • Provides care to members of other federally-recognized tribes who reside on the Flathead Reservation	PHC serves 15,000 patients in Missoula County • Approximately 52% of patients face economic insecurity • 29% of patients live at or below the federal poverty level • 7% of patients served identify as homeless • 17% of patients are uninsured	Psychiatric services for children and adolescents throughout Montana • Approximately ~4,000 patients served in 2020 • 70% children from families living at or near poverty • 39% of admissions referred from rural areas • 14.7% of admissions identified as American Indian • Medical genetics program serves prenatal, pediatric, and adult populations

Table 2.2. Participant Demographics (n=48)

Characteristics	
	Mean (range)
Age (years)	41 (28-73)
Years in Practice	9.5 (1.5-44)
Gender	n (%)
Female	32 (67%)
Male	16 (33%)
Clinical/Facility Role	n (%)
Physician	15 (31%)
Pharmacist	7 (15%)
Nurse Practitioner	8 (17%)
Physician Assistant	1 (2%)
Administration	5 (10%)
Information Technology	2 (4%)
Informatics	2 (4%)
Other	8 (17%)

Table 2.3. Opportunities to mitigate medication management concerns unique to neglected populations

Confederated Salish and Kootenai Tribes (CSKT)	Partnership Health Center (PHC)	Shodair Children's Hospital (Shodair)
"The dissemination of information from research centers to the frontlines of care delivery, especially in a frontier state like ours, is always a challenge, whether it's precision medicine or just [the] latest cancer protocols." —CSKT01, Physician "I think that there's…a misrepresentation [that current guidelines can be universally applied to people of all ancestries] in…both the [pharmacogenetics] research and also the literature of both management options and then also barriers that some [historically disadvantaged] communities face." —CSKT02, Physician	"I would say that our mission and vision is to provide high quality healthcare to everyone…the majority of our patients are folks who have a lot of struggles that they deal with on a daily basis, mostly socioeconomic-related, so whether they don't have insurance, they're homeless, the insurance they do have is really limited, they can't afford a lot of the premiums for certain treatment, and so breaking down those barriers is a huge part of the vision here." —PHC01, Pharmacist	"Sometimes when kids get here, they're on a lot of different medications, and so trying to get that down to a reasonable amount, whatever that might be [is the challenge]. You can imagine [the difficulty of] a seven-year-old trying to take seven different medications. Maybe with the right management, it could be [reduced to] three or four." —Shodair01, Administrator/Physician "A hard part that we see is kids leave here and they go back to rural communities especially, but even larger communities…some of the newer medications for some [patients] are kind of – I might use the word "scary" for some of our rural providers especially, and so they are nervous about prescribing those, so we try to give them guidance on [those medications]." —Shodair03, Administrator

Table 2.4. Potential barriers to pharmacogenetic implementation for underrepresented populations

Confederated Salish and Kootenai Tribes (CSKT)	Partnership Health Center (PHC)	Shodair Children's Hospital (Shodair)
"Some people feel that [genetics] is a potentially sensitive area, that maybe either people who shouldn't have access to that information might get access to that information or that people who are 'qualified researchers' may nonetheless ask research questions that are offensive to certain communities." —CSKT04, Pharmacist	"To our patient population, cost is always an important thing, so we have a tendency not to run tests unless they're going to be meaningful and make a difference in care. We don't want to be doing tests that are unnecessary or tests that have so many limitations that they're not useful." —PHC02, Physician/Administrator	"I think my only concern is that as long as there's good interpretation and there's enough support for those physicians that do order [pharmacogenetic] testing that they'd be able to interpret what those things mean." —Shodair04, Genetic Counselor
"I think working primarily with a native population and recognizing some of the research that has already been done, and I know first-hand that some of those genetic indicators are more represented in [the] Caucasian population so then the benefit of that technology has been to that larger [European] population." —CSKT02, Physician	"For a lot of people whose clinical life is already so complicated and hard and time-consuming, it's really stressful to think about adding something new, so I think just being really thoughtful about integrating it in a way that is going to seem palatable to that spectrum. […] Sometimes. It's just like, 'I can't deal with this other new thing'." —PHCO3, Physician	"That's probably one reason why I haven't used [pharmacogenetics] is because I don't feel like I could – as a family nurse practitioner, I didn't get specific training on it, so if I didn't precept or have somebody to work with who understood it well, there's no reason for me to order it." —Shodair06, Nurse Practitioner
		"One of the things is I would want to make sure that [pharmacogenetics is] available for all patients. Whenever we're making decisions, treatment decisions based on insurance, that doesn't feel good." —Shodair03, Physician

Table 2.5. Facilitators and perceived value of pharmacogenetic testing services targeted to underserved patient populations

Confederated Salish and Kootenai Tribes (CSKT)	Partnership Health Center (PHC)	Shodair Children's Hospital (Shodair)
"I do think [pharmacogenetic testing] has a place, particularly… for management of depression. My thoughts going forward is that I think it's a great opportunity. It's like all technology gets cheaper the longer we use it. If we can really dial in what it takes to get a chronic disease under control, whether it's diabetes or treat their colon cancer, I think it will be well received… I also think if you can really tailor medical therapy to be effective and, of course, we're going to improve health outcomes, which makes a lower cost of care, and less unexpected interactions within the medical system." —CSKT02, Physician "I'm all for minimizing medicine [polypharmacy] as best we can… That's kind of my end goal as a pharmacist." —CSKT05, Pharmacist	"Providing information about which test to order, to me, is [very] valuable because there's a lot of tests out there. And it's unclear to me which are most evidence-based, which are validated, and which provide clinically valuable information. If I'm going to order a [pharmacogenetic] test, I want to know what to do with those results. And I want that knowledge to enable me to make a decision that I wouldn't have been able to make otherwise or wouldn't have felt as good about making without that information." —PHC05, Administrator/Physician "The providers have to buy into it, that this would help make their practice better, enhance their practice, and see the benefit of how it would -- and then the rest of us could get onboard." —PHC04, Administrator	"Ideally, you see maybe a faster time to effective dose or maybe less trials before you get to a treatment that works really well. Those would be good outcomes. Maybe you could even look at hospital days [length of stay] That would be cool. I think those are the kinds of things that then you're talking people's language because you're saving money." —Shodair04, Genetic Counselor "I think rather than an entire [pharmacogenetics] report—because based on the ones I've seen previously and I'm sure this [new service] is a different test—that could end up being quite a stack of paper with all the recommendations. So I would like to see the recommendations first [and then details]. Of course, it would be nice if [pharmacogenetic test results] could just be uploaded into [the EHR]. I think that would make it easy for everyone to access." —Shodair09, Physician

Table 2.6. Role of a unique telehealth delivery model for pharmacogenetic consultation

Confederated Salish and Kootenai Tribes (CSKT)	Partnership Health Center (PHC)	Shodair Children's Hospital (Shodair)
Not addressed (secondary analysis)	"I really think that this type of a concept [telehealth consultation service] with the center in our state makes sense, and I think it makes sense to house it at the University of Montana. I think it's a really important opportunity that we need to be exploring… in five or ten years it's going to be very important… I think it's good for us to be ahead of the curve and start exploring this now." —PHC06, Pharmacist "Offering sometimes a hub for information is really helpful, […] that kind of warm line that we can call and say like, "Oh, this is the situation. This is my question." I think having that kind of point of care resource is really helpful." —PHC05, Administrator/Physician	"I think looking at providers around Montana, a [desirable] outcome for me would be the opportunity to become a really valuable resource to rural frontier providers so that they can refer to us [partnership between Shodair and University of Montana] for [pharmaco]genetics consults. But, if they can refer for pharmacogenetic testing [at Shodair], and if we can do it in a timely, cost-effective manner so they can make treatment decisions, then we become an invaluable partner to them." —Shodair05, Administrator

Chapter 3. Pharmacogenetics in Pediatric Psychiatry: Considerations for Implementation in Rural Communities

3.1 Introduction

Rapid advancements in pharmacogenetics have generated opportunities for healthcare providers to incorporate genetics into clinical decision-making and medication management using patient-specific data. Pharmacogenetic testing has enabled providers to individualize patient therapies and optimize medication prescribing in a variety of therapeutic areas. The Clinical Pharmacogenetic Implementation Consortium (CPIC) is an international leader in publishing pharmacogenetic guidelines that translate pharmacogenetic test results into actionable prescribing recommendations [125, 126]. CPIC has published guidelines in psychiatry that are primarily based on research in adult populations but include unique considerations for pediatric populations [127-130]. Research on using pharmacogenetics in pediatric psychiatric care is limited, but evidence is growing to support clinic utility [131-140].

With the promise and innovation offered by genomic medicine, academic medical centers and large health systems have begun to implement pharmacogenetics [141-149]. These efforts have not typically included rural, community-based health systems, which historically are the last to implement new medical advancements due to inadequate funding, shortage of expert personnel, geographic remoteness, and competing priorities [74]. Approximately one in five U.S. citizens reside in rural areas, and it is essential that implementation of new technologies does not leave these patients behind [150]. Pharmacogenetic testing is largely unavailable in rural settings for both adult and pediatric psychiatric patients, and this lack of access may exacerbate existing healthcare disparities. In the state of Montana, two out of three residents live in rural areas; the majority of the state is designated as medically underserved, with chronic shortages in primary care and with access to specialty care—including psychiatry—

remaining further out of reach [151, 152]. For instance, 55 of 56 Montana counties are designated as Health Professional Shortage Areas in mental health [152]. Montana continually has one of the nation's highest rate of suicide, a problem exacerbated by the lack of access to mental healthcare. Suicide remains one of the top causes of preventable death in Montana for children and adolescents, with 10% of students attempting suicide [153], an urban-rural disparity found across rural communities in the United States [154, 155]. Pharmacogenetic-guided prescribing for psychiatric medications in pediatric populations may provide enormous benefits in resource-limited rural communities.

In addition to healthcare disparities and inadequate access for rural patients, psychiatric care comes with its own unique set of challenges. Current clinical guidelines for psychiatric medications indicate starting patients on low doses, and slowly titrating up to therapeutic levels. Striking a balance between preventing adverse drug reactions, while maximizing potential benefits of treatment, is a crucial goal for providers in the psychiatric setting. Many psychiatric medications can take weeks, or even months, to work effectively, extending a difficult trial-and-error period of treatment selection for patients. Pharmacogenetic testing can help guide clinicians through initial drug prescribing by providing an evidence-based framework to modify what otherwise remains a mostly empirical and error-prone process. Developing pharmacogenetic testing interventions for smaller, community-based health systems must be a priority to ensure pharmacogenetics is delivered equitably.

While many providers serving rural and underserved communities are enthusiastic about the prospect of incorporating pharmacogenetics into their practice, implementation efforts have been uneven [81, 82, 84]. Creative solutions are needed to address

patients' limited access to emerging healthcare innovations such as pharmacogenetics. We aim to increase pharmacogenetic testing in these communities by establishing community-university partnerships and a centralized, statewide telehealth pharmacogenetic consult service at the University of Montana (UM). In preparation for piloting this intervention, we interviewed key stakeholders at Shodair Children's Hospital (referred to collectively as Shodair)—Montana's only psychiatric hospital for pediatric patients—to assess feasibility and provider interest. Further, we assessed the potential for remote telehealth pharmacogenetic consultation based at the UM. The barriers and facilitators identified here will inform pharmacogenetic implementation efforts at Shodair and provide a framework for engaging rural health systems across the country.

3.2 Materials and Methods

3.2.1 Research setting

Shodair (Helena, MT) is Montana's premier provider of inpatient and outpatient specialized psychiatric care for children and adolescents. Shodair also has a comprehensive medical genetics laboratory, providing genetic testing, clinical care, and expertise on genetic diseases and treatment to patients across the state. This research was approved by the UM Institutional Review Board.

Interest in establishing a pharmacogenetic testing program is not a novel idea for providers at Shodair. The genetics laboratory offered pharmacogenetic testing when the technology became feasible in the clinical setting several years ago. Uptake was limited, however, and providers cited the lack of evidence-based guidelines and uncertainty about proper clinical utilization of results as reasons for not using pharmacogenetic

testing at that time. Since Shodair's earlier use, pharmacogenetic testing platforms have become more comprehensive, cost has decreased substantially, and CPIC and other consortia have published standardized clinical guidelines in psychiatry [152].

3.2.2 Study design, data collection, and analysis

In order to assess the barriers and facilitators of implementing pharmacogenetic testing services at Shodair, key informants were asked to complete a brief survey and participate in semi-structured interviews. Prospective participants were identified with assistance from Shodair partners and subsequent snowball sampling. We recruited participants between August–December 2019. Recruitment stopped when researchers determined theoretical saturation had been reached [115]. Participants gave oral consent to participate in the study and did not receive compensation.

The survey gathered demographic information, information on the patient population, and general thoughts and experience using pharmacogenetic testing. Participants completed the survey prior to the interview without assistance from researchers, either on paper or online using Qualtrics (Provo, UT, USA).

Interviews were conducted in person at Shodair and lasted 30–60 minutes. Guided by constructs within the Consolidated Framework for Implementation Research (CFIR), members of the UM research group developed a written interview guide [114]. The guide included open-ended questions regarding Shodair's current medication management and prescribing practices, organizational priorities including their vision and mission, and outcomes of interest for pharmacogenetic testing. The interview also assessed participants' perspectives regarding resources required to support implementation of

pharmacogenetics, interpretation of test results, and prescribing recommendations. Interviews were audio recorded, transcribed, de-identified, and uploaded into ATLAS.ti (Berlin, Germany) for analysis. We performed a descriptive thematic analysis of the interview transcripts [116]. Members of the research team reviewed the transcripts independently to identify major themes and develop codes. Researchers used an iterative process of discussion, comparison, and consensus to refine codes. The resulting final codebook was evaluated collectively by all team members, and major themes and codes generated were analyzed for potential discrepancies and potential sources of bias.

3.3 Results

3.3.1 Participant demographics

We recruited 21 participants in this study with a range of ages, genders, and years in practice (Table 3.1). We sought to recruit participants from a variety of backgrounds in order to survey a range of clinical and administrative expertise.

3.3.2 Medication management challenges in the pediatric psychiatry setting

Participants identified several key challenges in medication therapy management for Shodair pediatric patients, including polypharmacy, side effect management, and treatment resistance. According to participants, particularly psychiatric providers, a significant concern was the high number of psychiatric medications these patients are prescribed either at the time of admission to Shodair or during their course of treatment at the hospital. Providers noted that while simplifying medication therapies and reducing

the number of medications prescribed could increase adherence upon discharge—providing an overall benefit to patients—de-escalating therapy can be difficult. Patients treated at Shodair come from all over Montana. After discharge from Shodair's main facility in Helena, many patients return home to their rural communities where adequate resources and access to mental health services to ensure continuity of care may not be available. For example, one provider stated,

> *I get concerned when children come in on multiple different medications, so I work really hard to try to simplify. I don't like them to be on a lot of medications, and I think that there's a tendency for that to occur within the community because [local providers are] trying really hard to manage them and they're willing to add [medications], but not take them off, out of fear that there might be some episode of deterioration [for the patients]. - PGX18, Nurse Practitioner*

Providers described balancing desired medication effects with potential side effects as another significant concern, noting that children with psychiatric disorders requiring inpatient treatment are often considered "treatment resistant." They cited medication failures as a potential driver for post-discharge nonadherence and future readmission. For instance, one provider described that a trial-and-error process is common because there is a lack of clear, straightforward psychiatric clinical guidelines for children and adolescents,

> *My biggest challenge is patients that come in with anxiety and depression and maybe some suicidal ideation and then you're really just picking one of many meds out of a magic hat and saying, 'All right, let's try it.' If they had a family member on a*

medicine, that's a better route to go […] but even that is not foolproof, and these medicines take so long to work, so you can't have them come back three days later and say, 'Are you feeling better?' because that's not a reliable expectation of the medicine, and so you have to wait a month. -PGX20, Nurse Practitioner

Potentially, pharmacogenetic testing can help mitigate these issues, providing further support and tools for providers in psychiatric care. As we present in later sections, most participants regard pharmacogenetic testing as a means to optimize therapy more quickly, so when patients return to their respective communities, they have a better chance at successful symptom management.

3.3.3 Barriers to pharmacogenetic implementation

Participants described a range of barriers, some of which were specific to Shodair's unique position as a rural pediatric psychiatric facility. These included issues regarding education on the benefits and limitations of pharmacogenetic testing, a lack of provider education and resources, integration of test results in the electronic health record (EHR), and challenges of transferring critical clinical information between facilities (e.g. Shodair and patients' community health systems).

Some participants who had experience with pharmacogenetic testing identified clear expectations for what pharmacogenetic testing services would look like at Shodair and how they would be presented to patients and providers. For example, one participant expressed, "[*Pharmacogenetic testing would] be great, I think in many ways. One of my major concerns about the testing is that I feel the public is given misinformation by [pharmacogenetic testing companies] about what [the test] actually can and can't do."-*

PGX04, Physician. Pharmacogenetics is a relatively new and evolving field, and many participants did not feel adequately prepared to use pharmacogenetic testing as a tool for clinical decision making. The majority of providers practicing at Shodair have not had formal pharmacogenetic training and will require education and resources before utilizing it to make clinical decisions in their practice.

Participants also cited issues with EHR integration and information transfer as a primary barrier to implementation.

> *[A] provider isn't going to know or even look [for pharmacogenetic results] unless the patient says, 'I've had [pharmacogenetic testing] done. Make sure you don't start a medicine that my body isn't going to metabolize right.' So, if a box [with pharmacogenetics results] came up, then the provider is forced to look at that box and check something before you can actually finish the prescription. -PGX20, Nurse Practitioner*

Shodair does not currently have the capability to integrate pharmacogenetic test results into their EHR system. As a smaller facility, Shodair licenses their EHR from a larger health system, so a technical modification to integrate pharmacogenetic data would need to be either purchased by Shodair or built in-house, both of which may be cost-prohibitive. Data transfer between Shodair and the patients' community healthcare facilities and providers is also a logistical concern. Participants shared ideas on how clinical decision support tools could support pharmacogenetic implementation within the EHR. Suggestions included an alert within the system, similar to those that flag allergies or potential drug-drug interactions, having a "special condition" listed within the patient profile, and flagging a patient's profile that notifies a prescriber when a patient has had a pharmacogenetic test.

3.3.4 Facilitators of pharmacogenetic implementation

Participants identified a number of factors that would facilitate successful implementation of pharmacogenetic testing at Shodair. Several providers identified pharmacists as the ideal “primary champions” for integrating pharmacogenetic testing into prescribing decisions and providing education and resources to providers on site. Additionally, participants cited access to pharmacogenetic expertise as a key factor in the effective utilization of test results. Participants shared that patients and patients’ families should receive education on the testing itself, what purpose it may serve, and how test results will be utilized to individualize their treatments.

Provider participants believed pharmacogenetic testing may have more success in the outpatient setting compared to acute, inpatient care. Previous use of pharmacogenetics at Shodair focused on testing patients upon admission. Due to long turnaround times, the results were often returned after patients had been discharged. Shodair has expanded outpatient services in recent years, attempting to bridge the gap between their inpatient services and patients who reside in the community. This offers providers an opportunity to focus on a preemptive, rather than reactive, approach to treatment resistance or treatment failure. Preemptive testing was preferred by the majority of participants.

3.3.5 Pharmacogenetic implementation aligns with the mission of Shodair

Staff and administrators noted that Shodair, a statewide leader in pediatric psychiatry—and home to the only medical genetics laboratory in Montana—is ideally positioned to

test the implementation of a pharmacogenetic testing program. One participant described the current outlook of pharmacogenetic implementation, stating, *"If you've got leadership in psychiatry and leadership in genetics and administration [as Shodair does], then you've really got the core team that you need to make it work and I think you're going to find strong board support for this. [The Shodair] board is quite fascinated by genetics" -PGX01, Administrator*. Personnel at Shodair from different fields of practice shared the belief that pharmacogenetic testing could allow providers to improve quality of care for their patients. This sentiment is summarized by one participant, "*As the providers […] one of our goals is to provide really the best psychiatric care in the state of Montana. And so, if this allows us to provide better care, then it absolutely aligns with what our providers are all trying to hope for and accomplish." -PGX15, Nurse Practitioner*

Participants praised Shodair's current expertise in medical genetics within their genetics laboratory and believed this to be a facilitator to providers readily adopting pharmacogenetic testing. Several participants spoke to the potential for pharmacogenetics to benefit children and adolescents suffering with mental illness in Montana, and described the opportunity to serve as a leader in pharmacogenetic testing as a positive outcome for Shodair and patients across the state.

3.3.6 Perceptions regarding telehealth pharmacogenetic consultations

We asked participants for their feedback regarding a centralized pharmacogenetic resource at the UM that would offer Montana providers pharmacogenetic consultations via a telehealth model. UM will offer guidance to providers on identifying patients to prioritize for pharmacogenetic testing and using test results to guide prescribing decisions. Providers at Shodair utilize telehealth visits for appointments and

consultations in other areas of the facility, such as the medical genetics laboratory. This method is beneficial for rural patients who would otherwise have to drive long distances to reach in-person appointments. The COVID-19 pandemic has only enhanced Shodair's use of telehealth technology to communicate with their patients and other providers. With Shodair's experience with telehealth, participants were optimistic about the utilization of telehealth for pharmacogenetics. This sentiment can be summarized in a quote by one participant, who stated,

> *One of the things that I'm kind of intrigued by is we're starting to develop outpatient telemedicine and the ability to discharge and manage kids, and specifically to manage their meds. If we could pair that with pharmacogenetic testing, that becomes a pretty powerful service to offer a rural state. – PGX02, Physician*

Participants also expressed positive perceptions regarding access to this remote pharmacogenetic resource at the UM. They reported that time and resources can be hard to come by for Shodair providers because they are the only psychiatric facility for children and adolescents in the state, further endorsing a partnership with a remote service. One participant stated,

> *Realistically, I think it will probably work better to outsource [pharmacogenetic consultations considering] time and manpower. […] Given what [Shodair] pharmacists and the providers need to handle right now, I don't know if that would be too much of a burden upon them to then learn all [about pharmacogenetics]. – PGX10, Molecular Technologist*

Another benefit reflected by participants was the use of telehealth to deliver pharmacogenetic test results is increasing availability to rural patients receiving care elsewhere in the state, who otherwise would not have access to this technology.

3.4 Discussion

Effective management of medication therapy for children and adolescents affected by psychiatric disorders is a well-known clinical challenge, which is further complicated in rural and underserved populations. Our partnership with Shodair illustrates the need for novel strategies to implement health innovations aimed at ensuring more equitable access for these populations. Our study highlights considerations that will be important in supporting pharmacogenetic implementation in pediatric psychiatry in rural communities including identifying unique barriers and facilitators to pharmacogenetic implementation for community-based health systems and leveraging telehealth to deliver pharmacogenetic consultations in resources-limited settings.

While participants in our study cited barriers to pharmacogenetic implementation that have been identified in previous qualitative studies—such as testing cost and turnaround time of results—our findings underscore the unique challenges facing providers and health systems treating underserved populations [141-149]. Participants at Shodair cited inadequate access to pharmacogenetic expertise as a barrier to implementation as well as challenges regarding psychiatric medication management such as polypharmacy, reluctance to de-escalate therapy, and complicated side effect profiles. Informed by their prior experience with pharmacogenetic testing, Shodair providers had clear views on potential barriers to implementation such as EHR integration, information transfer between Shodair and patients' community health systems, and insufficient resources and education for providers.

Our results demonstrate that Shodair stakeholders are enthusiastic about utilizing telehealth to integrate pharmacogenetics into prescribing decisions. A centralized resource at UM will provide telehealth pharmacogenetics consultations to Shodair providers and be a resource for providers across the state. Telehealth can overcome challenges to implementing pharmacogenetics in rural, community-based health systems, including inadequate funding, shortage of expert personnel and geographic remoteness. Our approach has the potential to increase access to pharmacogenetics for other underserved populations, such as minority groups and those of lower socioeconomic status. Inclusion of these groups into the revolution of genomic medicine will aid in addressing healthcare disparities for these patient populations.

We argue that pharmacogenetic testing and integration into clinical psychiatry services—available at facilities like Shodair—may provide more critical benefits than for patients treated at large health systems. Mental illness is a prevalent problem in Montana that disproportionally affects a vulnerable population: Montana's youth. Suicide consistently remains one of the leading causes of death in children and adolescents in Montana [150]. Rural areas across the United States have higher rates of suicide and mental health issues, which may be exacerbated by the lack of access to mental health services forcing patients to travel large distances for specialized care. Shodair is the only inpatient psychiatric facility in Montana serving children and adolescents, and it is important to note that this lack of specialty care for young people is not unique to Montana. For Shodair providers, it is essential to achieve the correct dose quickly, because patients may not receive specialty care when they return home to their rural communities. Pharmacogenetics gives providers the opportunity to choose the right dose for patients early in the treatment decision process. Montana is fortunate to have a pediatric hospital that integrates medical genetic and psychiatric expertise, and

implementing pharmacogenetics at Shodair has the potential to provide a higher standard of care to children across the state.

Limitations of our study include a small sample size and the possibility that results may not be broadly generalizable because Shodair is a unique facility treating a special patient population. We believe that our results are translatable to a variety of sites, however, because they highlight the importance of engaging underserved populations, and the providers who treat them, in order to ensure that pharmacogenetic testing and other emerging health innovations will benefit everyone regardless of ethnicity, geography, or socioeconomic status.

Our goal is to establish a centralized pharmacogenetic resource to provide access to pharmacogenetic testing, interpretation of results, and pharmacogenetic expertise for providers and patients across Montana. The results of our study will generate a framework for pharmacogenetic implementation strategies focused on connecting patients and providers in rural areas to testing and consultations, which can be a model for other states with a large proportion of residents living in rural communities. Throughout the last year, health systems throughout the United States have demonstrated remarkable adaptability in the face of the COVID-19 pandemic. Out of this adversity, telehealth technologies have served as a solution to providing care to patients with limited access due to quarantine protocols [156]. A future in which we can continue to merge clinical expertise with cutting-edge technologies is critical. Implementing pharmacogenetic testing with innovative telehealth delivery systems is a model to best serve the most vulnerable patients and to ensure that the benefits of pharmacogenetics are more broadly democratized.

Table 3.1. Participant Demographics (n=21)

Characteristics	
	Mean (range)
Age (years)	43 (28-64)
Years in practice	10 (0.5-26)
Sex	n (%)
Female	12 (57%)
Male	9 (43%)
Profession	n (%)
Nurse practitioner	5 (24%)
Physician	4 (19%)
Administration	4 (19%)
Molecular technologist	3 (14%)
Genetic counselor	2 (9.6%)
Dietician	1 (4.8%)
Information Technology	1 (4.8%)
Pharmacist	1 (4.8%)

Chapter 4. Discussion and Future Directions

My thesis research adds knowledge that will facilitate pharmacogenetic implementation in settings that serve underserved patients—particularly rural and tribal patients—by assessing challenges unique to these communities. In my thesis research, I have contributed to this effort with (1) a needs assessment study, where providers and other healthcare personnel were interviewed at three sites across Montana: CSKT, PHC, and Shodair; and (2) an in-depth analysis to begin planning for pharmacogenetic implementation at Shodair Children's Hospital. We assessed multiple sites in order to gain perspectives on varying underserved population groups. While our focus is in Montana, we envision this model will translate into facilities with similar populations who have experienced inequitable healthcare access across the US.

Advancements in pharmacogenomics have increased rapidly in the last 20 years, however, this has led to inequitable access to pharmacogenetic implementation for many patients. The majority of successful implementation programs have been based in academic medical centers or large health systems serving patients living in major metropolitan areas, leaving rural, community-based systems behind. Through my research, I aimed to identify key challenges and facilitators to pharmacogenetic implementation in rural, tribal, and other underserved healthcare settings in order to achieve equitable access to pharmacogenetics. The overall goal of this project was to gain insight into the unique barriers that rural health systems face and develop novel implementation strategies.

We established partnerships at three unique sites in Montana representing a mixture of underserved populations and conducted a thorough needs assessment with key stakeholders. The facilities we interviewed provided distinct insights into the catalysts that would initiate implementation efforts as well as the barriers they face that stall

innovation. Well-established obstacles to successful implementation include antiquated infrastructure, lack of EHR integration, limited access to pharmacogenetic specialists, and others. Our analysis found rural providers and their patients were not immune to these barriers, but we learned additional challenges unique to their practices that need to be addressed for successful implementation.

Results from CSKT participants centered on protection for tribal people in future pharmacogenetics research and ensuring equitable access for patients of tribal descent. Historically, tribal communities have experienced trauma as a result of unethical research practices, and this has resulted in participant resistance towards future genetic research efforts. Most significantly, CSKT participants expressed concern that current exclusions of AIAN patients from studies may jeopardize the clinical utility of pharmacogenetics if the tests are based on data from non-tribal populations. To address this, researchers must work with tribal communities to establish trusting relationships to increase the number of tribal patients participating in genomic research. As discussed in greater detail in Chapter 2, community-based participatory research offers an approach to engaging tribal communities in pharmacogenetics research. Participants stated a grassroots implementation effort done in collaboration with Tribal Council and Culture Committees would likely be accepted. Through our partnership with the CSKT, we will continue to develop research projects that fit the needs of the community and help to ensure equitable access to the benefits offered by pharmacogenetics.

Social determinants of health and the impact of socioeconomic status were primary concerns for participants at PHC, as many of their patients do not have a means to afford tests. Participants explained any clinical test needs to be done in a resourceful and meaningful way, and results need to make an impact on patient care.

Pharmacogenetic testing for these patients would need to be covered by insurance or be affordable for their patients to pay out-of-pocket costs. Despite these concerns, participants were enthusiastic about the use of pharmacogenetics and felt a centralized resource for expertise at SIHI would be beneficial for their patients and their providers.

Shodair is the only inpatient psychiatric facility in the state serving pediatric patients and the interview results displayed their unique circumstances in caring for some of Montana's most vulnerable patients. Participants from Shodair expressed strong concerns around medication management, including polypharmacy and continuity of care when rural patients return to their respective communities. They stated that pharmacogenetics could serve as an additional tool in choosing medications and dosing, perhaps achieving therapeutic benefit in a timelier manner for these patients. Additionally, they were excited about using telehealth technologies as a means to deliver pharmacogenetic consultations and receive pharmacogenetic education from experts based at SIHI at UM. The majority of participants were ready and willing to implement testing into their practice.

We identified clear challenges to pharmacogenetic implementation in Montana, however, participants expressed interest in the benefits that pharmacogenetic testing could bring to their patients. This included predicting the likelihood of adverse drug reactions and assisting in achieving therapeutic concentrations for certain medications. Pharmacogenetic testing assists providers in choosing optimal medication regimens for patients early in the treatment process. Investing in pharmacogenetics can reduce travel and costs for patients who would otherwise need multiple follow-up visits before achieving therapeutic symptom management. This is especially applicable to mental and behavioral health patients, who often undergo multiple medication trials that can take

weeks, even months, to reach maximum benefit. This was apparent in the interviews from Shodair where participants expressed choosing the right medication, at the right dose, and at the right time can optimize medication therapy management, and in turn, reduce provider and patient burden.

Through this research we determined that there is enthusiasm for a centralized resource based in SIHI to serve as a hub for pharmacogenetic expertise. Shodair is the ideal site to begin implementation due to their prior experience with pharmacogenetics, readiness to utilize clinical pharmacogenetics, and enthusiasm for the implementation program. Pharmacogenetics experts at SIHI will provide telehealth pharmacogenetic consultations with therapeutic recommendations to Shodair providers utilizing pharmacogenetic test results, current medications, and other patient-specific factors. Additionally, teleconferencing will be used to provide pharmacogenetic education to providers and other staff. The recent expansion of telehealth services and internet accessibility in Montana promise to make the program successful. The COVID-19 pandemic has made telehealth more accessible, which also makes the program more feasible. We will continue to assess the benefits of using telehealth for pharmacogenetic implementation delivery, and the successes and pitfalls of our program will be analyzed to guide future efforts in implementation for rural, tribal, and other underserved communities.

Our goal is to serve as a model for other rural, tribal, and other underserved communities to reach their most vulnerable patients. These populations are often left behind when implementing novel healthcare technologies. The incredible benefits of genomic research should not be limited to urban, affluent populations who are largely of European descent. Underserved populations need to be represented and advocated for. Through our research in Montana, we hope to inspire other researchers to utilize CPBR

and implementation research, and ensure underserved communities have the opportunity to begin pharmacogenetics programs in their facilities. As researchers, we have the opportunity to give these populations a voice. Everyone, regardless of geographic location, socioeconomic status, tribal affiliation, or ancestry deserves access to health innovations.

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