AN ASSESSMENT OF BARRIERS TO NURSE PRACTITIONERS' UTILIZING PHARMACOGENETIC TESTING FOR DEPRESSION

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DOCTOR OF NURSING PRACTICE

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ABSTRACT

As a leading cause of disability worldwide, depression is considered a chronic disease. Medication management is the first-line treatment for moderate to severe major depressive disorder. Medications are selected based on provider experience and preference with a trial-and-error" approach. These medications may take several weeks to reach therapeutic dosing. If it is not tolerated or ineffective for treating the disease, then the medication regimen is changed, requiring a minimum of 4-6 weeks to determine efficacy. This trial-and-error approach to depression treatment can lead to patients living with persistently debilitating depressive symptoms for months, increased healthcare costs due to continued need to seek medical follow-up, or patients discontinuing care due to lack of efficacy early in treatment attempts.

In a post-market release study regarding the efficacy of antidepressant use, results indicated that 11% of the United States population takes an antidepressant. Depressed patients that do not benefit from the first antidepressant they are prescribed is 60% (Alemi et al., 2021). Pharmacogenomic testing (PGT) is beneficial in disease management by determining individual genotype responses to specific medications. Incorporating PGT into routine care for depression can lessen the time it takes to reach disease remission as well as avoid any adverse medication effects. Despite the known benefits of PGT, it continues to have a slow adoption rate in clinical practice.

Nurse Practitioners (NPs) surveyed aided the co-investigator in assessing current rates of NPs utilizing PGT as well as identifying barriers to use. Understanding limits for using PGT can contribute to developing targeted education in hopes of enhancing the uptake of PGT for managing depression into routine clinical practice. use. Understanding limits for using PGT can contribute to developing targeted education in hopes of enhancing the uptake of PGT for managing depression into routine clinical practice.

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LIST OF ABBREVIATIONS

ANA.....American Nurses Association

CDC .....Centers for Disease Control and Prevention

CI.....Confidence Interval

CPIC.....Clinical Pharmacogenetics Implementation Consortium

CYP.....Cytochrome P

DNA.....Deoxyribonucleic Acid

DOI .....Diffusion of Innovation

FDA .....Food and Drug Administration

GUIDED .....Genomics Used to Improve Depression Decisions

HGP .....Human Genome Project

ISONG .....International Society of Nurses in Genetics

IM.....Intermediate Metabolizer

MDD .....Major Depressive Disorder

NDNPA.....North Dakota Nurse Practitioners Association

NM .....Normal Metabolizer

NP .....Nurse Practitioner

NDSU.....North Dakota State University

NSDUH.....National Survey on Drug Use and Health

PD .....Pharmacodynamics

PGT .....Pharmacogenomic Testing

PharmGKB.....Pharmacogenomics Knowledgebase

PK .....Pharmacokinetics

PM.....Poor Metabolizer

RCT.....Randomized Control Trial

RM .....Rapid Metabolizer

SNRI .....Serotonin and Norepinephrine Reuptake Inhibitors

SSRI .....Selective Serotonin Reuptake Inhibitors

TAU .....Treatment As Usual

TCA.....Tricyclic Antidepressants

TRD.....Treatment-Resistant Depression

URM .....Ultra-Rapid Metabolizer

WHO .....World Health Organization

CHAPTER 1: INTRODUCTION

Background and Significance

Spanning from 1990 to 2003, with funding from the National Institute of Health, the Human Genome Project (HGP) allowed scientists to create the first sequence of the human genome. They defined a genome as "an organism's complete set of DNA" ((NHGRI), 2022). Information obtained from this project provided beneficial insight into tailoring the treatment of diseases based on one's genetic makeup. Pharmacogenomic testing (PGT) analyzes the genomic structure of the patient and allows healthcare providers to individualize patient pharmacotherapy without using a "one size fits all" approach to pharmacologic prescribing ((NHGRI), 2022). Mental health conditions specifically can be difficult to treat as patients' responses to first-line psychotropic treatment options may differ because of pharmacogenomic variations.

Pharmacogenomic testing has previously presented several barriers to prescribing providers that limit its ability to be used in clinical practice. Barriers noted to implementing testing include cost, lack of guidelines surrounding testing and implementation, interpretation of results, lack of time to educate patients on the benefits of testing, and lack of both provider and patient knowledge regarding PGT (Luzum et al., 2021). When used correctly, PGT can reduce economic and disease burdens for those diagnosed with debilitating health conditions, specifically mental health disorders requiring pharmacotherapy.

Mental health disorders affect people across the lifespan. One common mental health disorder that can cause significant dysfunction and disability is depression. The World Health Organization (WHO) endorses depression as a leading cause of disability worldwide and a significant contributor to the global disease burden. Depression is the persistent feeling of sadness as well as a loss of interest in activities that interfere with daily life ((WHO), 2021). Depression affects the overall well-being of the individual, and if not successfully treated, can be

life-threatening. Data obtained from the 2021 National Survey on Drug Use and Health (NSDUH) revealed that "…21.0 million adults in the United States had at least one major depressive episode. This number represented 8.3% of all U.S. adults" ((NIH), 2021, Prevelance section). Medical intervention along with treatment adherence is crucial in the management of depression. Time to reach therapeutic drug levels with proper medication regimens for mental health disorders can cause significant delays in disease remission. Lake and Turner (2017) found that "on average, it takes almost 10 years to obtain treatment after symptoms of depressed mood begin, and more than two-thirds of depressed individuals never receive adequate care" (Lake & Turner, 2017). Psychotropic medications are often necessary for individuals diagnosed with Major Depressive Disorder (MDD) to remain functional in their daily lives. A systematic review conducted by Semahegn et al., (2020) found high rates of non-adherence to psychotropic medications contributed to disease burden. Significant barriers to the use of psychotropic medications in controlling MDD included socioeconomic factors resulting in discontinuation before recommended treatment duration, misuse of medication due to lack of medication counseling, and individual beliefs regarding medication (Lake & Turner, 2017).

The Food and Drug Administration (FDA) recognized the positive correlation between genetic variations and response to treatment options. ((FDA), 2018)In a statement released in 2018, the FDA released guidance on how to accelerate the implementation of reliable and beneficial genetic testing into practice. The FDA recognized that to translate data from the Human Genome Project into useful practice, reliable references would need to be utilized. ClinGen was endorsed by the FDA through this guidance statement and continues to serve as an important database for variant evaluation, aiding researchers to incorporate findings into current everyday practice. Since the FDA's final guidance, pharmacogenomic information is included

on high-risk medication labels. Execution of PGT in clinical practice remains slow regardless of the known benefits ((FDA), 2018).

Problem Statement

Despite known and effective treatment options available, depression continues to cause disability. Medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first-line treatment options in the management of moderate to severe MDD. These medications may take several weeks to reach therapeutic dosing. A trial period of several weeks is needed for each medication regimen attempted, and switching to a different medication type or dosage is needed if the current regimen is not successful. This trial-and-error approach to depression treatment can lead to patients living with persistently debilitating depressive symptoms for months, increased healthcare costs due to the continued need to seek medical follow-up, or patients discontinuing care due to lack of efficacy early in treatment.

Results in a post-market release study regarding the efficacy of antidepressant use indicated that 11% of the United States population takes an antidepressant. Depressed patients that do not benefit from the first antidepressant they are prescribed are 60% (Alemi et al., 2021). Identifying barriers to the underutilization of PGT may help identify strategies to increase the uptake of PGT testing in the clinical setting to reduce time to antidepressant efficacy. PGT testing is often only pursued after several failed medication trials. When striving to reach remission of disease and avoid relapse, selecting the best medication to use based on individual genomics may lead to quicker remission of depressive symptoms and promote treatment adherence.

Purpose

The purpose of this project is to determine barriers for Nurse Practitioners (NPs) utilizing PGT as well as assess current rates of PGT when treating patients with MDD for those surveyed. Identifying barriers can lead to intervention strategies to improve patient and clinician uptake of PGT testing in the clinical setting for individuals diagnosed with major depressive disorder.

Objectives

The objectives of this DNP project are:

1. Identify current rates of utilization of pharmacogenomic testing amongst nurse practitioners responsible for the treatment of depression.
2. Determine barriers to nurse practitioners utilizing pharmacogenetic testing for prescribing psychotropic medications used to treat depression.
3. Evaluate nurse practitioners' level of confidence in utilizing pharmacogenomic testing.

CHAPTER 2: THEORETICAL FRAMEWORK AND LITERATURE REVIEW

A thorough literature review was conducted to examine the use of pharmacogenomics and prescribing mood-stabilizing medications. Multiple databases were searched, including PsychARTICLES, PsychINFO, PubMed, EBSCO, National Human Genome Research Institute, Access Medicine, and Google Scholar. North Dakota State University's research librarian aided in the literature search. Keywords included: pharmacogenomics, utilization of pharmacogenomics, barriers to utilization of genomic testing, genomics, psychotropics, depression, and barriers to treatment of depression. Inclusion criteria included literature published within the last 5 years, adult population (aged 19+), diagnosis of depression only as classified by the American Psychiatric Association in the diagnostic and statistical manual of mental disorders ((APA), 2022) and genomic testing. Articles that were not relevant to genomics and/or pharmacotherapy for depression management, published before 2017, and included participants younger than age 19 were excluded.

List of Definitions

Depression

Depression is a mental health diagnosis consisting of prolonged periods of sadness or loss of interest in things one typically enjoys. Individuals must have at least five of the nine symptoms listed below to classify depression. To meet the diagnostic criteria for depression, the symptoms listed below must have been present most of the day, nearly every day, for 2 weeks. Adults diagnosed with depression who have met the criteria outlined below will be the focus of this research focused on pharmacogenomic testing.

Table 1

Diagnosis of Major Depression.

Number	Item
1.	Depressed mood
2.	Anhedonia (lack of interest or pleasure in almost all activities)
3.	Sleep disorder (insomnia or hypersomnia)
4.	Appetite loss, weight loss; appetite gain, weight gain
5.	Fatigue or loss of energy
6.	Psychomotor retardation or agitation
7.	Trouble concentrating or trouble making decisions
8.	Low self-esteem or guilt, recurrent thoughts of death, or suicidal ideation

Note. Adapted from Table 26-1 in *Behavioral Medicine: A Guide for Clinical Practice, 5e*. by Raj Y, & Christensen J.F., & Feldman &.D. Depression. Feldman M.D., & Christensen J.F., & Satterfield J.M., & Laponis R(Eds.). Copyright 2020 by McGraw-Hill Education. (https://accessmedicine-mhmedical.com.ezproxy.lib.ndsu.nodak.edu/content.aspx?bookid=2747&sectionid=230250553)

Pharmacogenomics

Pharmacogenomics (PGT) is defined by the National Human Genome Research Institute (2022) as: "a component of genomic medicine that involves using a patient's genomic information to tailor the selection of drugs used in their medical management" (Teri Manolio, 2023). Researchers at the Pharmacogenomics Knowledgebase (PharmGKB) define pharmacogenomics as the "relationship between genetic variation and response to medicine" (M. Whirl-Carrillo, October 2012).

Psychotropics

Psychotropics are a broad category of medications that treat a variety of mental health conditions. Psychotropic categories include antidepressants, anti-anxiety medications, antipsychotics, stimulants, and mood stabilizers. For this project, psychotropics will mainly refer to antidepressants.

Literature Review

Pharmacogenomic Testing

Pharmacogenomic testing provides insight into the genetic structure of an individual and how they will respond to specific medications. Pharmacogenomics rapidly expanded in 1990 because of deoxyribonucleic acid (DNA) technology advancements and the HGP. Individual genetic variations can determine whether there will be a therapeutic response to medications or adverse reactions. Pharmacogenomic testing allows prescribers the ability to individualize patient treatment without applying a trial-and-error approach. Individualized drug therapy is dependent on specific biomarkers and the rate to which individuals metabolize, or process, these drugs. Genetic variations can influence whether an individual is a poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM) rapid metabolizer (RM), or ultra-rapid metabolizer (URM). Poor metabolizers may have higher levels of drug concentrations in their bloodstream due to enzymes inability to properly breakdown medication for use. Conversely, ultra-rapid metabolizers have lower drug concentrations in their bloodstream as their increased enzyme activity rapidly processes the medication. According to the Centers for Disease Control and Prevention (CDC), "Adverse drug events cause approximately 1.3 million emergency department visits each year. About 350,000 patients each year need to be hospitalized for further treatment after emergency visits for adverse drug events" ((CDC), 2017). Implementation of

pharmacogenetic testing before prescribing medications can improve patient safety and reduce the financial burden on hospital systems and patients.

Pharmacogenomic testing is performed by acquiring DNA from an individual. DNA is obtained from participants either through a blood draw or a buccal swab and submitted to the preferred PGT company. After analysis, it is reported whether the patient is at risk for gene-drug, and drug-drug interactions. Results indicate whether they are PM, IM, NM, RM, or URM of specific medications.

Pharmacogenetics and Major Depressive Disorder

Pharmacokinetics (PK) includes the absorption, distribution, metabolism, and excretion of the drug. Pharmacodynamics (PD) includes biochemical and physiological responses to a drug. Cytochrome P450 (CYP450) enzymes are responsible for a major role in the hepatic clearance of drugs. Evidence shows that genetic variations of CYP genes contribute to both PK and PD of medications (Peña-Martín et al., 2022).

Two of the P450 cytochromes that are endorsed as contributing to PD and PK of commonly prescribed antidepressants are CYP2C19 and CYP2D6. Meta-analysis and systemic review of 12 randomized control trials performed by Arnone, et. al, (2022), concluded that to be clinically relevant, PGT to treat MDD must include CYP2C19 and CYP2D6 as they are responsible for a majority of metabolism in SSRIs and TCAs. The review also found that providers were not likely to perform PGT on patients with an initial diagnosis of depression. Patients with treatment-resistant depression (TRD) or those who have failed at least three medications were ordered PGT to guide further disease management. Individuals who had PGT testing done to aid in medication management were found to have higher remission rates when

compared to those who utilized the trial-and-error approach with a confidence interval (CI) of 1.23-2.76 (Arnone et al., 2023).

Barriers to Utilizing Pharmacogenetic Testing

Barriers found to impact the uptake of pharmacogenetic testing are identified through the literature and grouped into themes. These themes include: cost, educational, available guidelines, and personal beliefs of both patients and providers.

Cost as a Barrier

The uptake of PGT is influenced by both the patient and the provider. Increasing popularity in recent years has made pharmacogenomic testing more readily available and cost-effective for patients to complete through either direct-to-consumer or clinically provided methods. Privately, or direct-to-consumer, completed PGT raises concern for the validity and accuracy of results as well as potential errors in the interpretation of findings as it bypasses healthcare clinicians' oversight. Some healthcare systems have adopted their form of commercial pharmacogenomic testing offered to patients and available within the electronic health record (EHR), thus eliminating the concern for testing validity.

A systematic review completed by Jameson, et al (2021), found the biggest perceived barrier to the utilization of PGT for patients to be financial reasons. This review included seven studies from the United States. Study participants cited that they would be more likely to complete PGT if insurance covered all, or part, of PGT (Jameson et al., 2021).

Depression increases healthcare utilization both directly and indirectly. A study conducted by Maciel et. al, (2018) aimed to evaluate cost savings associated with pharmacogenetic testing to guide treatment for depression. The study found that the economic burden in the United States for the management of depression costs $210.5 billion per year. This

number factored in both the costs of medical appointments and prescriptions as well as the loss of revenue due to individuals' occupational absence or disability as a result of their mental illness. Healthcare costs individuals acquired while seeking treatment for depression were evaluated using data from "a private insurance company with over 69 million beneficiaries from 69 large, self-insured US companies" (Maciel et al., 2018). When utilizing pharmacogenomic testing to guide treatment for depression, per-patient savings were found to be $5,962 (Maciel et al., 2018).

Providers' Clinical Experience with PGT

Limited knowledge surrounding pharmacogenomic testing and its implications for use was found to impact providers' utilization of PGT. Data from the literature demonstrated that healthcare professionals' inexperience and comprehension of pharmacogenomics directly impact their uptake of PGT (Fleming, 2020; Frigon, et al., 2019). PGT education on pharmacogenomics is integrated into other coursework such as pharmacology. The extent of pharmacogenomic education received varies by the school curriculum. Basyouni and Shatnawi, 2020, surveyed a variety of medical schools and found that "80.9% of responding schools currently teach the topic as part of another course and spend less than 10 didactic hours on the subject per term" (Basyouni & Shatnawi, 2020).

Additionally, the lack of disease-specific guidelines for implementing PGT is cited as a significant barrier to use by healthcare providers. In an evidence review completed by Luzum et al. (2021), 10,000 U.S. physicians were surveyed regarding pharmacogenomic testing and its implications for practice. Of those surveyed, 10% reported feeling adequately informed about pharmacogenomics, while "…70% believed that access to pharmacogenetic data would improve their ability to care for patients. However, only 30% responded they were confident in their

ability to use the results, and only 32% said they could find or use reliable sources of pharmacogenetic information while caring for patients" (Luzum et al., 2021). Furthermore, 100% of respondents surveyed endorsed the availability of guidelines, or lack thereof, as the main factor in deciding whether to implement PGT (Luzum et al., 2021).

The American Nurses Association (ANA) and International Society of Nurses in Genetics (ISONG) released a publication in 2012 titled: *Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees.* This publication provided a scope of practice for NPs outlining professional practice and professional responsibilities stating that "nurses with graduate degrees need to be able to provide personalized care and/or care coordination that incorporates genetic/genomic based technology into client care" (Greco et al., September 2011). It is expected that providers utilize genomic testing to guide clinic practice as outlined in this report. The literature review failed to find supportive data differentiating between NPs and physicians' utilization of pharmacogenomics in practice due to data on the two groups commonly categorized together in the surveys reviewed by the co-investigator.

Implementation in Primary Care

Statistically significant data obtained from randomized control trials are preferred for implementing evidence-based practice into clinical care. RCTs addressing pharmacogenomic testing are limited. Of the few RCTs that address PGT, small sample sizes contribute to low evidence ranking. Randomizing patients in an RCT when there is a known pharmacogenetic variant that may contribute to adverse outcomes poses an ethical dilemma. Retrospective studies or alternative forms of trial designs (such as case studies with n=1) need to be considered when guiding the implementation of PGT in clinical practice. Evidence from non-randomized clinical studies was utilized when the FDA opted to add pharmacogenomic information to drug labels.

There are now over 250 medications, some with black box warnings, that contain pharmacogenetic information on the label (Bradley et al., 2018; Health, 2020; Luzum et al., 2021; Research, 2019; Zanardi et al., 2021).

Uniformity on guidelines for implementing information obtained through PGT will allow clinicians to better incorporate results into patient care. Clinical Pharmacogenetics Implementation Consortium (CPIC) utilizes laboratory data from PGT to publish guidelines after completing a thorough, peer review process of potential interactions. Through CPIC guidelines, recommendations for several medications are made specific to the patient based on genotype or predicted phenotype. The CPIC has published recommendations for 106 gene-drug pairs that require action when prescribing. Guidelines from several pharmacogenomic research groups are available through the database on PharmGKB for providers to incorporate test results into patient care (Abdullah-Koolmees et al., 2020).

Guidelines found on PharmGKB specific to antidepressants include 33 medications under the classification of antidepressants. Of those 33 antidepressant medications, 37 drug label annotations contain existing genotype/metabolizer data and recommendations based on phenotype. Guidance for providers prescribing these medications is found within package inserts and includes the following recommendations based on the individual's phenotype: “Testing required”, “Testing Recommended”, “Actionable PGx” and “Informative PGx” (Whirl-Carrillo et al., 2023).

Success Rates for MDD Treatment with Psychotropic Medications

Current treatment modalities for depression are based on clinicians’ personal preferences and experience, which may include psychotherapy, antidepressant medication, or a combination of both. With the use of PGT, pharmacokinetics, pharmacodynamics, and gene-drug interactions

can be factored into medication selection. PGT including Cytochrome P450 (CYP450) isoenzymes, specifically phenotypes CYP2C19 and CYP2D6, are largely responsible for the metabolism of psychotropic medications. Randomized control trials (RCT) comparing individuals diagnosed with MDD utilizing PGT to guide treatment versus treatment as usual (TAU) were found to have both significantly improved responses to treatment as well as higher rates of disease remission (Bradley et al., 2018; Greden et al., 2019; Zanardi et al., 2021).

The Genomics Used to Improve DEpression Decisions (GUIDED) trial in which all study participants received active treatment was completed over 24 weeks. Participants had to have failed at least one medication trial and be over the age of 18. The study cohort included a total of 1398 participants. When assessed at week 8 of the study, PGT-guided treatment patients had symptom improvement ($p=0.036$), treatment response ($p=0.002$), and remission ($p=0.066$) when compared to TAU cohorts. Rates of remission for PGT-guided study participants doubled between weeks 8 and 24 of the study (Greden et al., 2019).

The RCT trial with 579 adult participants was conducted by Bradley et. al (2017) found that PGT-guided treatment for depression significantly improved response to treatment ($p=0.001$) and improved remission rates ($p=0.02$) as compared to the control group (Bradley et al., 2018).

Summary

In 2017, there were 847 licensed NPs in North Dakota, with 79% of those being certified in Family Practice (Owens & Zwilling, 2020). This number continues to rise. Data from the 2020-2021 Annual Report released by the North Dakota Board of Nursing (NDBON) concluded that there were 1,549 licensed Nurse practitioners with full practice authority in the State of North Dakota (Nursing, 2020-2021). A majority of chronic diseases are managed by Primary

Care NPs, including MDD, as it continues to be a leading cause of disability worldwide. Current practice for managing MDD relies on provider preference and experience. Incorporating PGT testing into routine care for managing depression could improve patient outcomes and decrease the economic burden this disease continues to cause. Despite its many benefits, PGT continues to have a slow rate of adoption into current clinical practice.

To increase the utilization of pharmacogenomic testing to aid in the treatment of MDD, one must first understand why it is often excluded as routine practice before prescribing medications to manage MDD. Assessing Nurse Practitioners' current rates of PGT utilization in treating MDD as well as identifying barriers that hinder the implementation of PGT into routine care is a necessary step to promote the uptake of PGT.

Theoretical Framework

Everett Rogers' Diffusion of Innovation (DOI) Theory was used as the framework to guide the development of this project. According to Rogers (2003), innovation "is an idea, practice, or object that is perceived as new by an individual or other unit of adoption" (Rogers, 2003). Diffusion is defined as "the process by which an innovation is communicated through certain channels over time among the members of a social system" (Rogers, 2003). Both innovation and diffusion are essential in promoting the utilization of PGT to guide medical care for individuals diagnosed with MDD. Using Rogers' DOI theory, the co-investigator will be able to identify barriers that prohibit NPs from implementing PGT into clinical practice.

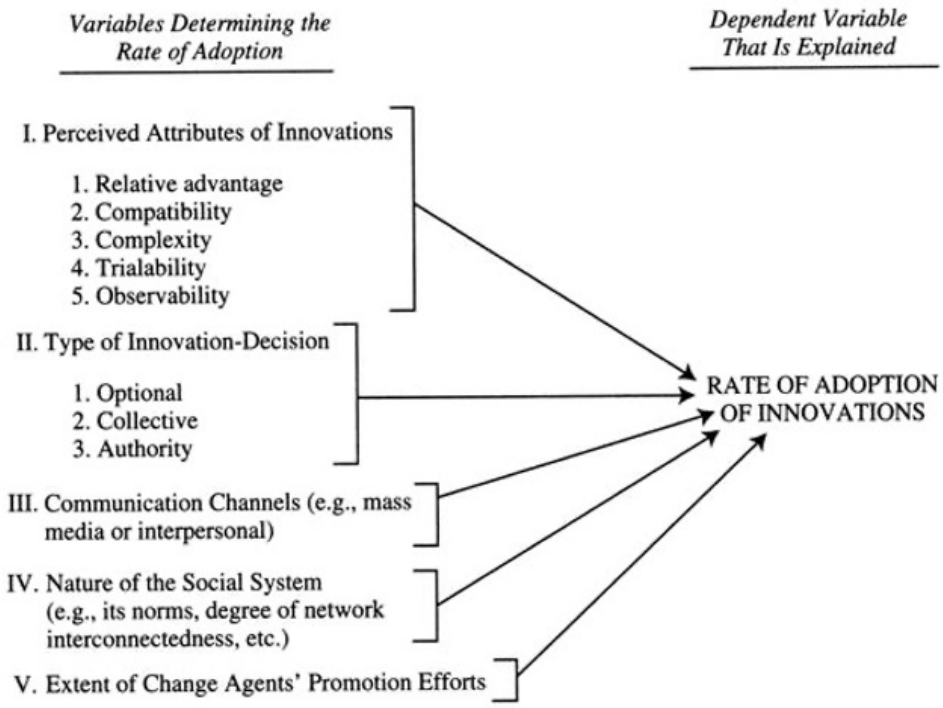
Diffusion of Innovation

Rogers' theory outlines four main elements: innovation, communication channels, time, and a social system. The rate of adoption of an idea is dependent on the characteristics of innovation. Communication is required for an innovation to spread within the social system.

Social systems can include individuals, groups of individuals, organizations, or subsystems within an organization. Rogers utilizes several figures to depict the DOI theory. In one figure, Rogers outlines the variables that exist when determining the rate of adoption.

Figure 1

Variables Determining the Rate of Adoption



There are many known benefits of pharmacogenomic testing, so why is it not used more often to guide the treatment of debilitating conditions, such as MDD? The DOI outlines perceived attributes of innovations to include five categories: relative advantage, compatibility, complexity, trialability, and observability.

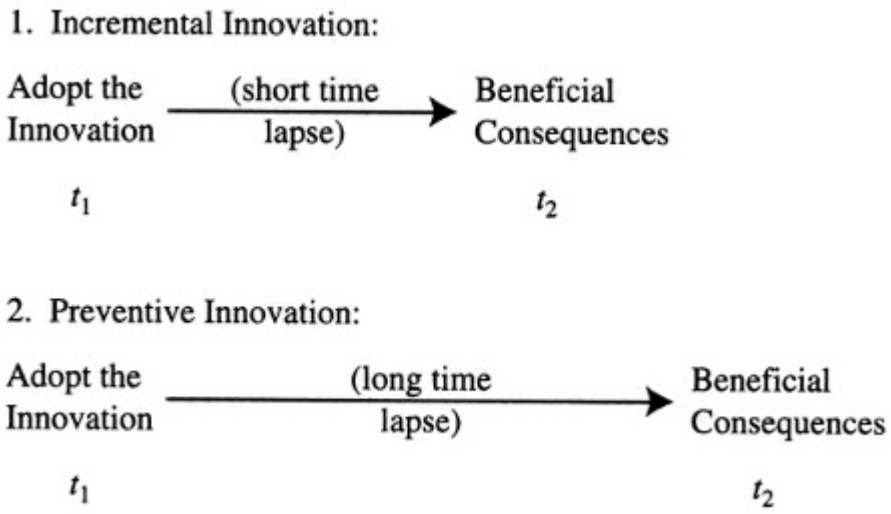
Relative Advantage

Relative advantage includes cost, status, and over adoption. Relative advantage can be further broken down to include innovations that are *incremental* and *preventative*. Rogers states that "Preventative innovations is a new idea that an individual adopts now in order to lower the

probability of some unwanted future event" (Rogers, 2003). On the other hand, incremental innovations "provides a desired outcome in the near-term future" (Rogers, 2003). Incremental innovations have a higher rate of adoption due to instant gratification, as depicted in Figure 2.

Figure 2

Incremental versus Preventative Innovation



Pharmacogenomic testing can be classified as a preventative innovation. While not every individual may experience undesired effects from medications, individuals with genetic variants known to alter the pharmacokinetics of drugs may benefit from utilizing PGT.

Compatibility

An innovation may be accepted or rejected based on compatibility. This includes compatibility with sociocultural values and beliefs, previous innovations, and/or the need for innovation. Proper implementation of an idea is required to avoid negative associations with the projected innovation. In terms of pharmacogenomic testing, past experiences with treating MDD may cause providers to reject the innovation of utilizing genomic testing for prescribing practices. The current practice of a stepwise approach for managing depression may prevent providers from using PGT before starting psychotropic medications. It is not until previous

treatments have failed that one may consider utilizing PGT. The co-investigator will determine if compatibility is a hindrance to ordering PGT.

Complexity

Perhaps the greatest barrier to the adoption of PGT is the complexity of its use. As outlined in the review of literature; interpretation of results, provider experience, and lack of guidelines for use all negatively correlate with the adoption of employing PGT into routine clinical practice. The complexity involved with pharmacogenomics and its implication for meaningful use may impede provider's willingness to adopt this innovation.

Trialability

According to Rogers (2003): "*Trialability* is the degree to which an innovation may be experimented with on a limited basis." (Rogers, 2003)Trialing of innovations allows users to give meaning to an idea and tweak it to personal or systemic needs. PGT is relatively easy to obtain, but prescribing based on results requires providers to know how to interpret results.

Observability

Innovations that are easily visible to individuals are positively correlated with the rate of adoption. Assessing barriers to the utilization of PGT may promote exposure to the vast benefits of precision medicine and guide future pharmacogenomic education.

Summary

Rogers' Diffusion of Innovation theory guides this project by identifying the rationale for why NPs may not be utilizing PGT when it is known to improve patient outcomes with treating MDD. The relative advantage, complexity, compatibility, trialability, and observability must all be addressed to improve rates of adoption for the employment of PGT into routine clinical practice.

CHAPTER 3: METHODS

Overall Project Design

This project's purpose was to determine barriers to pharmacogenetic testing to improve the uptake of PGT testing in the clinical setting for individuals diagnosed with major depressive disorder. The study collected quantitative data through an online survey employed at the Fifteenth Annual North Dakota Nurse Practitioners Association (NDNPA) pharmacology conference for NPs who chose to willingly participate. In addition to being dispersed at the pharmacology conference, the survey was sent via hyperlink to NPs who voluntarily chose to partake in the survey through word-of-mouth communication. The survey assessed providers' educational background, area of practice, duration of practice, and lastly, knowledge, beliefs, and implications for use regarding PGT. Refer to Appendix B for survey questions. Everett Roger's Diffusion of Innovation theory will guide the implementation of this quality improvement initiative through the following objectives:

1. Identify current rates of utilization of pharmacogenomic testing amongst Nurse Practitioners responsible for the treatment of depression.
2. To determine barriers to nurse practitioners utilizing pharmacogenetic testing for prescribing psychotropic medications used to treat depression.
3. Evaluate nurse practitioners' level of confidence in utilizing pharmacogenomic testing.

Setting

The setting of this project took place at the Fifteenth Annual NDNPA Pharmacology Conference located in Bismarck, North Dakota. The conference was held between the dates of September 20-22, 2023 with options to attend in-person, virtually, or both in-person and virtual. Project participation included all NPs in attendance and was not limited to North Dakota NPs. Recruitment for NP participation also included a poster presentation, handouts with directions to

accessing online surveys, and spoken communication among peers. In addition, the social media liaison for the NDNPA committee dispersed the same infogram containing the survey link and QR code to all members of the NDNPA via e-mail and social media webpage.

According to NDNPA board member, Dr. Allison Peltier, the 13th annual NDNPA pharmacology conference had 305 attendees. The 14th annual NDNPA had 305 attendees both virtual and in-person included. The 14th annual conference had 38 attendees from Minnesota, three from South Dakota, one from Montana, one from California, and one from Oregon, with the remainder from North Dakota (Entzel 2023).

Sample/Sample Size/Recruitment

An online Qualtrics survey was developed to determine the correlation between education level, provider experience, and current knowledge surrounding PGT and barriers to use (See Appendix B). Recruitment of participants occurred through infographics provided during the NDNPA Pharmacology conference. Hyperlinks to complete the Qualtrics survey were provided to virtual attendees. An email and social media post including both hyperlinks and infographics was dispersed to NPs that are members of the NDNPA through the NDNPA social media liaison. Consent was obtained and confirmation of NP licensure was confirmed by participants prior to survey question advancement. Upon survey completion, a free text option allowed participants to provide an e-mail address if they wished to receive study results as well as receive further educational resources to enhance uptake in the utilization of PGT for clinical management of MDD.

Implementation Plan

The online Qualtrics survey aided in identifying barriers to the use of PGT. The survey design replicated a similar questionnaire developed by the Psychiatric Pharmacogenomics Laboratory at the University of Calgary targeting pediatric psychiatrists as well as pediatricians (See Appendix D). Although the reliability and validity was recognized as a limitation of their study, the questionnaire aided in the development of the co-investigators survey (Jessel et al., 2022). Survey questions were formatted to provide inferential statistical data among NPs with differing demographical backgrounds. Utilization of both Likert scale and binary questions were included in the survey to meet the project objectives. Demographical information asked in the survey included the following: gender, age, years of clinical practice, area of clinical practice, current state of practice, type of degree (master's or doctorate) as well as type of program degree obtained through (online versus in-person). Further survey questions were formatted to evaluate potential obstacles to employing PGT to enhance the treatment of MDD. Generalized binary questions evaluated NPs' attitudes, beliefs, prior knowledge of PGT, and current practicing facilities' uptake of PGT results.

The conference took place between the dates of September 20-22d, 2023 on campus at Bismarck State College within the National Energy Center for Excellence building with online participants viewing live via an online platform funded by the NDNPA.

Infographics containing the QR code to take the survey were placed on each table in addition to being e-mailed and posted to social media for all members of the NDNPA through the NDNPA social media liaison. Briefly written education will be shared via e-mail to study participants upon final defense. Education will include the benefits of PGT, incidence of

depression, of incorporating PGT into clinical treatment for MDD, and hyperlinks to obtain more information on PGT Education.

Evaluation/Outcomes/Data Analysis

Participants were given ten days between the dates of September 20th through September 30th to complete the survey. Upon survey closure, results were evaluated to determine if the project objective of identifying potential barriers to uptake of PGT was met. Data was stored online through co-investigators password-protected OneDrive through North Dakota State University (NDSU). Utilization of the North Dakota State University Statistics Department aided in data analysis. To aid in data analysis, Microsoft Teams was used with access granted to committee members and participating students from the NDSU statistics department. No personal identifiers were shared during this process. Data results in addition to further educational resources about PGT and benefits for use in MDD will be sent to study participants who provided e-mail contact information upon completion of final defense.

Protection of Human Subjects

The human subjects involved in this project are practicing Nurse Practitioners working in primary care or psychiatric practices. Participation was completely voluntary and did not require any patient identification. Participants who are not advanced practice providers were excluded from this study. The statistics obtained did not require and/or use any personal identifiers. Protection of human subjects occurred through the North Dakota State University Institutional Review Board.

CHAPTER 4: RESULTS

Survey Response

A total of 33 participants accessed the survey. Survey responses were eliminated if the participant did not hold NP licensure (*n=4*), they did not select "yes" to consent to the survey (*n=1*), or they did not complete the survey in its entirety (*n=5*), thus leaving a sample size of 23 individuals (*n=23*) for data analysis using measures of central tendency. The majority of survey responses were submitted by females (*n=21*) practicing primarily in family medicine(*n=17*) with licensure in North Dakota (*n=17*). Primary areas of clinical practice by other survey participants included psychiatry (*n=3*) and other (*n=3*). Ages ranged from 31 to "over 60" and were grouped by the following: 31-39 (*n=11*), 40-50 (*n=8*), >50 (*n=4*). When asked how many years they have been an NP, two participants reported practicing between 1-5 years (*n=2*), 11 participants between 6-10 years (*n=11*), and 10 participants had over 11 years (*n=10*) of experience as an NP. Nurse practitioners with both doctorate (*n=14*) and masters (*n=9*) education levels participated in the survey.

Objective One

The first objective aimed at identifying the current rates at which nurse practitioners utilize pharmacogenomic testing to aid treatment for depression. Questions 14 and 15 assessed the broad use of pharmacogenomic testing while questions 16 and 17 determined if providers utilized PGT specifically for depression treatment. Survey questions and responses are demonstrated in Table 1.

Table 2

Current Rates of PGT Utilization

Survey Question	Sample Size
Have you ever ordered a pharmacogenomic test?	
Yes	n =13 (56.52%)
No	n =10 (43.48%)
How many times would you estimate that you have ordered a pharmacogenomic test in the previous 12 months?	
1-4	n = 6 (46.15%)
5-10	n = 5 (38.46%)
11-20	n = 2 (15.39%)
Of those times, have you ordered pharmacogenomic testing to manage major depressive disorder?	
Yes	n = 10 (76.92%)
No	n = 3 (23.08%)
Unsure	n = 0 (00.00%)
Have you ever offered a patient pharmacogenomic testing after failing several antidepressant medication treatments?	
Yes	n = 14 (60.87%)
No	n = 7 (30.43%)
Does not apply to my practice	n = 2 (08.70%)

Objective Two

Objective two focused on specific barriers that hinder nurse practitioners from utilizing PGT testing when prescribing psychotropic medications for depression. Questions 11, 12, and 13 were asked to determine awareness of PGT through both patients and practicing facilities. Of the 23 NPs surveyed, 78.26% (*n=18*) reported that patients have asked them about pharmacogenomic testing. Thirteen NPs surveyed (56.52%, *n=13*) work at facilities that offer PGT with the majority (59.09%, *n=13*) of those facilities lacking guidelines for utilizing PGT. Questions 8 and 9 identified the extent to which education impacted the uptake of PGT by providers. Providers' personal beliefs surrounding PGT were assessed as a barrier in questions 18 and 19. Survey results are outlined in Table 2 below.

Table 3

Barriers

Education	n (%)
Have you received formal education (graduate course work, continuing education) related to utilizing pharmacogenomics in clinical practice?	
Yes	n = 20 (86.95%)
No	n = 1 (04.35%)
Unsure	n = 2 (08.70%)
If yes, did your education on pharmacogenomic testing include indications for use in treating Major Depressive Disorder (MDD)?	
Yes	n = 12 (52.17%)
No	n = 11 (47.83%)
Personal Beliefs	**n (%)**
Do you believe pharmacogenomic testing can improve outcomes in individuals diagnosed with depression?	
Yes	n = 20 (86.96%)
No	n = 1 (04.35%)
Unsure	n = 2 (08.69%)
I feel that pharmacogenomic testing would aid in treating individuals diagnosed with major depressive disorder.	
Strongly disagree	n = 2 (08.70%)
Somewhat disagree	n = 3 (13.04%)
Neither agree nor disagree	n = 0 (00.00%)
Somewhat agree	n = 8 (34.78%)
Strongly agree	n = 10 (43.48%)

The extent to which assumed barriers impacted nurse practitioners utilizing pharmacogenetic testing for prescribing psychotropic medications used to treat depression was addressed in questions 20 and 21. Results are displayed in Figures 3 and 4 below.

Figure 3

Barriers that NPs Believe Hinder the Utilization of PGT to Guide Depression Treatment

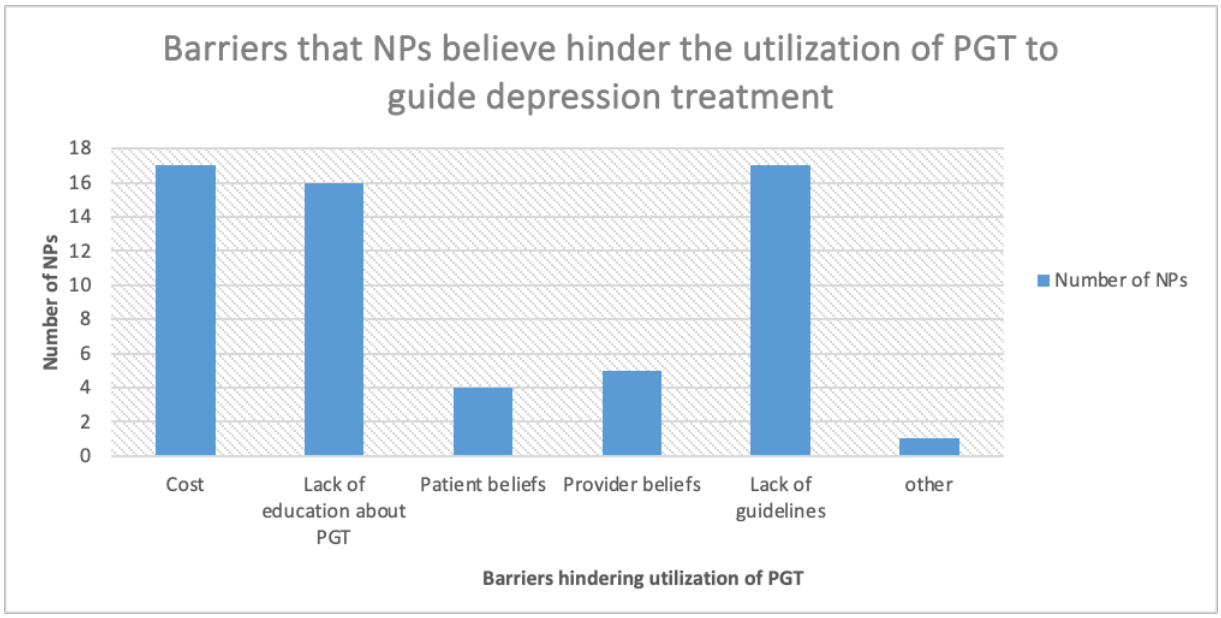
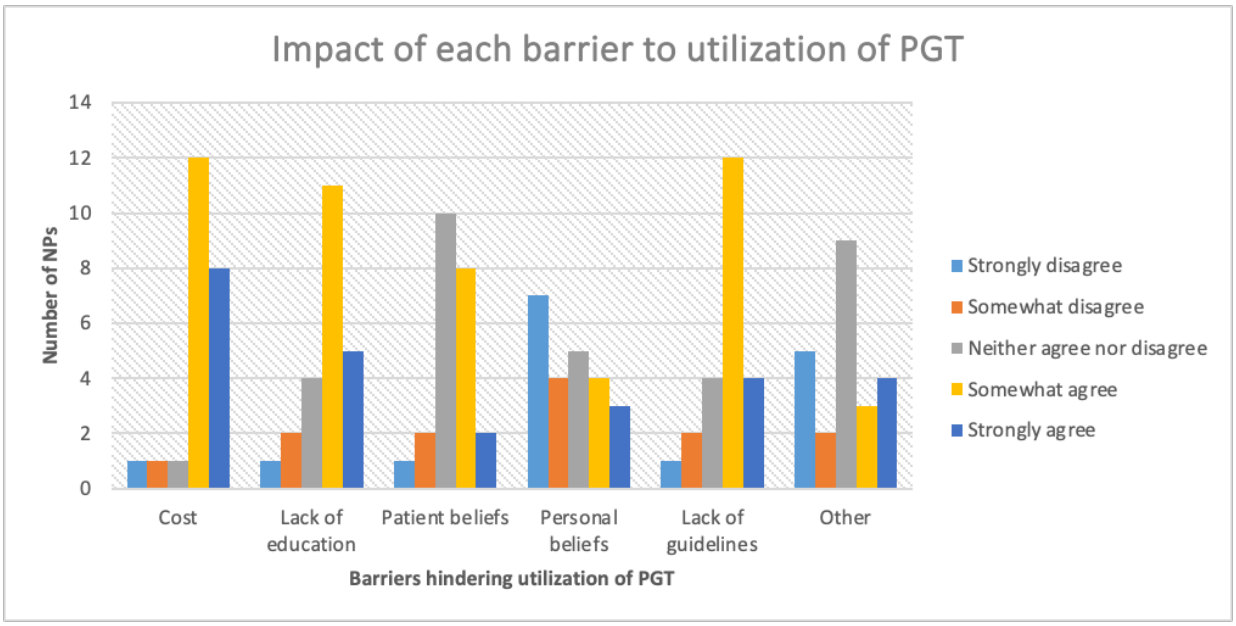


Figure 4

Impact of Each Barrier to Utilization of PGT

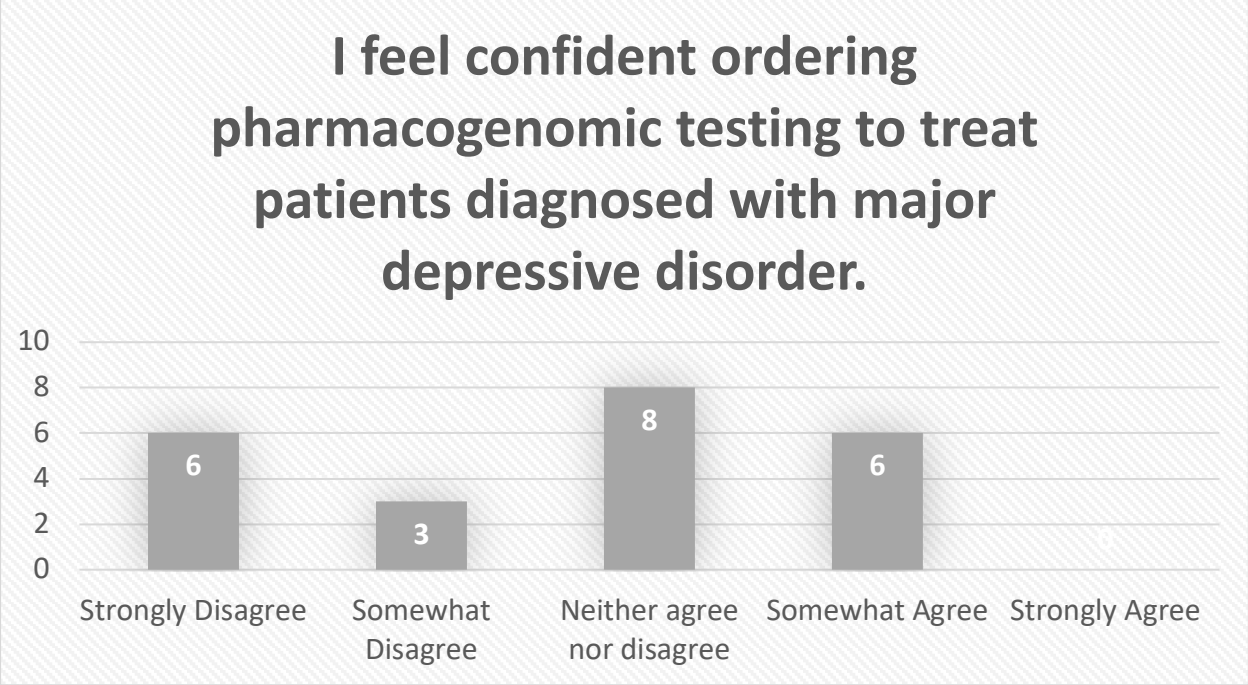


Objective Three

The third objective evaluated nurse practitioners' level of confidence in utilizing pharmacogenomic testing to treat patients diagnosed with MDD. Question 10 directly met this objective with participants ranking the following statement: "I feel confident ordering pharmacogenomic testing to treat patients diagnosed with major depressive disorder". The majority (*n=8*, 34.78%) of participants selected "*neither agree nor disagree*", and zero participants chose "*strongly agree*" regarding their confidence in ordering PGT to treat MDD. Objective three is depicted in chart format in figure five below.

Figure 5

Confidence Levels



Note: Total sample size was 23.

CHAPTER 5: DISCUSSION AND RECOMMENDATIONS

Literature has shown that integrating pharmacogenomic testing in treatment plans for individuals diagnosed with depression contributes to improved patient outcomes and quality of life (Alemi et al., 2021; Arnone et al., 2023; Jameson et al., 2021). Despite these findings, the adoption of PGT into clinical practice remains slow. This study utilized both quantitative and qualitative data to determine NPs current rates of utilizing PGT to manage treatment for individuals diagnosed with depression. Additionally, NPs confidence levels and perceived barriers hindering the use of PGT for treating MDD were evaluated.

Summary

Participants' survey responses aligned with common barriers limiting PGT use identified during the literature review. A systematic review conducted by Jameson, et al (2021) concluded that financial reasons were the greatest perceived barrier to utilizing PGT (Jameson et al., 2021). Data results from this survey correlated positively with literature findings as 73.91% (*n=17*) of NPs cited cost as a significant contributor that limits their use of PGT within clinical practice for MDD treatment. Coincidentally, the lack of uniform guidelines for implementing PGT into clinical practice ranked identical (73.91%, *n=17*) to potential cost by NPs surveyed. A Likert scale was developed to identify the extent to which specific barriers impacted respondents' use of PGT with the following selections: strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, and strongly agree. When considering barriers, eight (34.78%) selected "*strongly agree*" and 12 (52.17%) chose "*somewhat agree*" that potential cost impacted their utilization of pharmacogenomic testing in clinical practice. Twelve out of 23 (52.17%) individuals reported they "*somewhat agree*" that a lack of uniform guidelines for implementing PGT into clinical practice limits their use of testing, while four (33.33%) reported they "*strongly agree*" with this statement.

During the survey, the educational background of NPs was collected. A majority (n=14, 60.86%) of those surveyed were doctorate-prepared NPs who attended hybrid programs (both online and in-person). Twelve of the 23 study participants (52.17%) acknowledged receiving formal education, including both coursework and continuing education, regarding pharmacogenetics and pharmacogenetic testing to treat depression. Despite having training, 69.56% of NPs surveyed endorsed a lack of education surrounding PGT as a hindrance to their utilization of PGT within clinical practice.

An evidence review by Luzum et al. (2021), reported that 70% of providers felt access to PGT results would improve their ability to care for patients, 30% felt confident utilizing results obtained from genetic testing and 100% cited the availability of guidelines or lack thereof, as the main deciding factor on implementing PGT in clinical practice (Luzum et al., 2021). Over half (n=13, 56.52%) of the NPs surveyed reported their facility lacks guidelines for utilizing PGT. Among the 23 participants, 86.95% confirmed that they believe utilizing PGT to guide depression treatment can improve patient outcomes. However, only 26.09% (n=6) expressed being "*somewhat confident*" in ordering PGT to treat MDD, and an equivalent percentage (26.095, n=6) "*strongly disagree*", indicating they lack confidence in ordering genetic testing. Overall, study respondents predominately (n=8, 34.78%) selected that they "*neither agree nor disagree*" regarding their confidence levels in ordering PGT to guide MDD.

Discussion

Guided by Roger's Diffusion of Innovation (DOI) theory, pharmacogenomic testing to guide treatment for depression was the constant variable in this study. Considering the DOI attributes: relative advantage, compatibility, complexity, trialability, and observability; study participants were asked several questions regarding their demographics, educational background,

personal beliefs, and clinical experience as it pertains to PGT. Factors impacting barriers to adopting PGT into routine practice were evaluated and compared to the literature upon the survey's completion.

In comparison to previous research, subjects reported potential cost as one of the main perceived barriers hindering the use of PGT in routine clinical practice. Recently published literature in the Canadian Medical Association Journal by Ghanbarian, et al (2023), evaluated both the effectiveness and cost-savings associated with PGT. Through systematic reviews, analyses of administrative data, and expert judgment, researchers found that "the overall cost savings from a public payer perspective was estimated to be $956 million over the 20-year-time horizon or a cost savings of $4926 per patient" (Ghanbarian et al., 2023, Results section). Additionally, this study concluded through sensitivity analyses that within 2 years of implementing PGT, initial costs would be offset. To address potential costs associated with PGT as a barrier, both healthcare providers and patients must consider the long-term financial benefits rather than the upfront costs of completing testing.

Of the surveyed participants, the lack of uniform guidelines for use within practice hindered their utilization of PGT to guide MDD treatment to the same extent as potential costs. Literature review findings concluded healthcare professionals' clinical adoption of PGT was influenced by the shortage of data from RCTs and a lack of concise, consistent guidelines (Lim et al., 2023). While the CPIC database does provide generalized guidelines for how to use genetic test results for drug therapy, it fails to provide clinicians insight into which test to order and how to incorporate testing into routine practice.

Evaluation of existing literature indicated that a knowledge deficit surrounding PGT and its implications for use also contributed to infrequent use. Results from the co-investigator's

survey aligned with data findings with most participants citing lack of education surrounding PGT as a barrier. Surprisingly, over half of the NPs reported receiving formal education on PGT and PGT to treat MDD. Confidence level was not directly linked to education in this regard, as responses varied among NPs surveyed. Contrary to literature findings, results from this study found that participants conveyed neutral feelings when asked to rank their confidence level for utilizing PGT to treat individuals diagnosed with MDD.

Recommendations

To promote the widespread adoption of PGT for the management of MDD, systemic changes must occur. Educational curriculums for healthcare clinicians must be evaluated to ensure teachings on PGT include implications for use, interpreting results, available resources, collaborating with pharmacists, and insights to providing patient education. Additionally, individual healthcare providers may seek out further educational opportunities to obtain credentialing in genomic studies or continuing education courses to narrow the knowledge deficit. As an emerging field, several resources to enhance clinicians' knowledge of genomics are provided through the National Human Genome Research Institute.

By familiarizing themselves with the benefits of PGT, specifically PGT for MDD treatment, clinicians can enhance knowledge and therefore improve confidence levels. Recommendations for future projects include creating disease-specific guidelines or algorithms for utilizing PGT in clinical practice, evaluating the extent of NPs' formal education surrounding PGT, and identifying other barriers that were not listed within the survey. Literature findings are limited when discussing the cost of PGT within the United States. A cost analysis of PGT within clinical practice may also provide an opportunity for further projects. Furthermore, the NDNPA

may aid in knowledge enhancement of PGT by recruiting keynote speakers specialized in the study of genomics.

Strengths and Limitations

To reach primary care NPs across the state of North Dakota, collaboration with the organizers of the largest NP gathering in the state was a strength of the project. Deploying the project with the NDNPA at their annual pharmacology conference offered the best opportunity to reach a substantial number of practicing NPs to recruit for participation. Pharmacists and researchers with expertise in pharmacogenomics were included on the committee. Their ability and input on the project created a strong project design, identified barriers to be addressed before implementation, and helped with the understanding of the significance and limitations of the project results.

A few limitations of this project were found. Current literature did not delineate between types of providers, their understanding, and use of PGT so there is no ability to compare findings to other studies nor find if this work was previously completed. While the project was specific to NPs, the sample size ended up being smaller than anticipated and lacked diversity in both demographics and practice-setting. A limitation of the survey was not including a free text area for participants to describe other barriers outside of those listed. One participant identified "other barriers" that were not cited as a potential barrier to implementation.

Dissemination

Findings from this study will be disseminated through the executive summary (See Appendix E). The executive summary will be dispersed to participants who provided email as well as to all members of the NDNPA through the use of the social media liaison of the NDNPA.

Upon the final defense's completion, this project will also be published through the North Dakota State University Thesis and Dissertations database.

Conclusion

Current treatment modalities for depression include medication and/or psychotherapy. Psychotropic medications prescribed to manage depression require time to reach therapeutic levels within the body and trial and error to find medication best suited to individual patient needs. Mental health conditions, including depression, continue to be the leading cause of disability worldwide as reported by the WHO. With several known benefits, precision medicine can lessen the disease burden that depression causes. By identifying barriers that influence NPs decision to utilize PGT to treat MDD, we can aim to enhance the utilization of genomic testing to improve patient outcomes.

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APPENDIX A: IRB APPROVAL

NDSU NORTH DAKOTA STATE UNIVERSITY

08/25/2023

Dr. Carrie Ann Nelson
Nursing

Re: IRB Determination of Exempt Human Subjects Research:
Protocol #IRB0004879, "AN ASSESSMENT OF BARRIERS TO NURSE PRACTITIONERS UTILIZING PHARMACOGENETIC TESTING FOR DEPRESSION"

NDSU Co-investigator(s) and research team:

- Carrie Ann Nelson
- Sierra Entzel
- Natasha Jean Petry
- Allison Evelyn Peltier
- Kristine Jayne Steffen

Approval Date: 08/25/2023
Expiration Date: 08/24/2024
Study site(s): 15th annual NDNPA pharmacology conference as well as online through e-mail communications and social media (facebook) account held by the NDNPA.
Funding Source:
The above referenced human subjects research project has been determined exempt (category 2) in accordance with federal regulations (Code of Federal Regulations, Title 45, Part 46, *Protection of Human Subjects*).

Please also note the following:

- The study must be conducted as described in the approved protocol.
- Changes to this protocol must be approved prior to initiating, unless the changes are necessary to eliminate an immediate hazard to subjects.
- Promptly report adverse events, unanticipated problems involving risks to subjects or others, or protocol deviations related to this project.

Thank you for your cooperation with NDSU IRB procedures. Best wishes for a successful study.

NDSU has an approved FederalWide Assurance with the Department of Health and Human Services: FWA00002439.

RESEARCH INTEGRITY AND COMPLIANCE
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APPENDIX B: SURVEY

1. Gender:
    - Male
    - Female
    - Other
    - prefer not to answer
2. Age: _____
    - Prefer not to answer
3. How many years have you been a Nurse Practitioner? _____ years
4. Are you a specialty provider or family medicine?
    - Family medicine
    - Pain
    - Oncology
    - Cardiology
    - Psychiatry
    - GI
    - Other:_____
5. Type of degree:
    - Masters
    - Doctorate
6. Type of graduate program:
    - Online
    - In-person
    - Hybrid (online and in-person)
7. State that you are currently practicing in?
    - ND
    - SD
    - MN
    - MT
    - Other_____

PHARMACOGENOMICS:

8. Have you received formal education (graduate course work, continuing education) related to utilizing pharmacogenomics in clinical practice?
    - Yes
    - No
9. If yes, did your education on pharmacogenomic testing include indications for use in treating Major Depressive Disorder (MDD)?
    - Yes
    - No

10. Please answer the following:

	Not at all confident	Slightly confident	Neutral	confident	Very confident
How confident would you be to order pharmacogenomic testing to manage patients diagnosed with major depressive disorder?					

11. Has a patient ever asked you about pharmacogenomic testing?
    - Yes
    - no
12. Does your facility offer pharmacogenomic testing?
    - Yes
    - No
    - unsure
13. Does your facility have guidelines for utilizing pharmacogenomic testing?
    - Yes
    - No
    - Unsure
14. Have you ever ordered a pharmacogenomic test?
    - Yes
    - No – If no, skip to question 16.
15. how many times would you estimate that you have ordered a pharmacogenomic test in the past12 months? _____
16. Of those times, have you ever ordered pharmacogenomic testing to manage major depressive disorder?
    - Yes
    - No
    - Unsure
17. Have you ever offered a patient who has failed several antidepressant treatments pharmacogenomic testing?
    - Yes
    - No
    - Does not apply to my practice
18. Do you believe pharmacogenomic testing can improve outcomes in individuals diagnosed with depression?
    - Yes
    - No
    - Unsure
19. If you answered yes to the previous question, please rank the following statement:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I feel that pharmacogenomic testing would aid in treating individuals diagnosed with major depressive disorder					

20. What barriers do you feel are hindering utilization of pharmacogenomic to guide treatment for depression? *Select all that apply*
    - o Cost
    - o Lack of education surrounding pharmacogenomic testing
    - o Patient beliefs
    - o Provider beliefs
    - o Lack of uniform guidelines for use within practice
    - o Other _____

21. Select how much do you agree or disagree with the following statements:

	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
Potential **cost** impacts my utilization of pharmacogenomic testing in clinical practice	○	○	○	○	○
Lack of **education** surrounding pharmacogenomic testing impacts my utilization of pharmacogenomic testing in clinical practice.	○	○	○	○	○
Patient beliefs surrounding pharmacogenomic testing impact my utilization of pharmacogenomic testing in clinical practice	○	○	○	○	○
My personal beliefs as a provider impact my utilization of pharmacogenomic testing in clinical practice	○	○	○	○	○
The **lack of uniform guidelines** for implementing pharmacogenomic testing in clinical practice limit my use for testing results	○	○	○	○	○
There are **other** barriers that were not mentioned that impact my utilization of pharmacogenomic testing in clinical practice.	○	○	○	○	○

APPENDIX C: PHYSICIAN SURVEY

Jessel CD, Maruf AA, Oomen A, Aronld PD, Bousman CA. (2022). Pharmacogenetic testing knowledge and attitudes among pediatric psychiatrist and pediatricians in Alberta, Canada. *Journal of the Canadian Academy of Child and Adolescent Psychiatry,* 31: 18-27.

QUESTIONNAIRE

INFORMATION:

The purpose of this questionnaire is to assist in the implementation of pharmacogenetic testing to inform antidepressant, antipsychotic, anxiolytic, and mood stabilizer prescribing among children and adolescents. This questionnaire was developed by the Psychiatric Pharmacogenomics Laboratory at the University of Calgary.

We will not ask you information that personally identifies you and we ask that you not to share personal data in this questionnaire. Through our selected software setting we configured this questionnaire so that your responses are anonymous. For this reason, the data tables from our database do not contain any information about who completed the survey.

Neither you nor your clinical practice will be adversely affected if you decline to participate in this study.

☒ I confirm my agreement to participate

About You:

How many years of clinical experience do you have?

- Currently in training
- 0-4
- 5-10
- 10-19
- 20-29
- Over 30

Main care setting:

- Inpatient
- Outpatient
- Inpatient and outpatient
- Non-clinical

Main work location:

- Urban
- Rural
- Urban and Rural

Where did you complete your psychiatry residency?

- Canada
- USA

- Outside of Canada/USA

What best describes your specialty? (select all that apply)

- Addiction
- ADHD
- Anxiety disorders
- ASD or other Neuorodevelopmental disorders
- Eating disorders
- Forensic
- Mood disorders
- Psychotic disorders
- General child psychiatry
- Other (Specify):

Your Experience with Pharmacogenetic Testing

Before starting with the questionnaire, please answer the following questions regarding your experience with pharmacogenetic testing.

1. Have you ever ordered/recommended pharmacogenetic testing?
    a. Yes
    b. No → skip to 4

2. How often do you order/recommend pharmacogenetic testing?
    a. Rarely
    b. Sometimes
    c. Routinely

3. In your career, how many pharmacogenetic tests have you ordered/recommended?
    a. < 10
    b. 10 - 50
    c. 51 - 100
    d. >100

4. Has a patient ever come to an appointment with pharmacogenetic testing results that you did not order?
    a. Yes
    b. No

5. Has a patient ever asked you about pharmacogenetic testing?
    a. Yes
    b. No

6. Have you ever attended a course, workshop, or seminar related to pharmacogenetic testing?

a. Yes
b. No

7. How familiar are <u>you</u> with pharmacogenetics?

    a. Not at all familiar
    b. Not very familiar
    c. Somewhat familiar
    d. Very familiar
    e. Extremely familiar
    f. Prefer not to answer

8. How familiar are <u>your colleagues</u> with pharmacogenetics?

    g. Not at all familiar
    h. Not very familiar
    i. Somewhat familiar
    j. Very familiar
    k. Extremely familiar
    l. Prefer not to answer

9. Which of the following pharmacogenetic resources are you familiar with? (Select all that apply)
    a. Clinical Pharmacogenetic Implementation Consortium
    b. Royal Dutch Pharmacogenomics Working Group
    c. Canadian Pharmacogenomics Network for Drug Safety
    d. Pharmacogenomics Knowledgebase (PharmGKB)
    e. Pharmacogene Variation Consortium (PharmVar)

Please rank your level of disagreement/agreement with each of the following statements using the following scale:
1-3: I disagree with the statement (the lower the score, the greater the level of disagreement).
4-6: I neither agree nor disagree with the statement; I do not have a well-defined criterion on the issue (choose 4 if closer to disagreement, 5 if undecided, or 6 if closer to agreement).
7-9: I agree with the statement (the higher the score, the greater the level of agreement).

	Disagree <----------> Neither <----------> Agree								
Topic 1. Indications for Pharmacogenetic Testing	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1.1 In children and adolescents, pharmacogenetic testing improves the efficacy of psychotropic medications									
1.2 In children and adolescents, pharmacogenetic testing reduces the risk for adverse drug reactions related to psychotropic medications									

1.3 In children and adolescents, pharmacogenetic testing is clinically useful	**Skip to 2.1**								
1.4 In children and adolescents, pharmacogenetic testing should be used to inform psychotropic medication:									
1.4a selection									
1.4b dosing									
1.4c switching									
1.4d augmentation									
1.4c deprescribing									
1.5 In children and adolescents, pharmacogenetic testing should be offered:									
1.5a …prior to starting psychotropic medications									
1.5b …after non-response to 1 or more psychotropic medications									
1.5c …after the onset of an adverse drug reaction or intolerable side effect related to a psychotropic medication									
1.5d …to patients with treatment-resistant conditions									
1.5e …if recommended by Health Canada or the FDA									
1.5f …if a pharmacogenetic dosing guideline is available for the drug being considered									

	Disagree <----------				**Neither**				**Agree** ---------->
Topic 2. Barriers and Facilitators of Pharmacogenetic Testing	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
2.1 There is not enough clinical evidence for me to use pharmacogenetic testing in my practice									
2.2 Lack of reimbursement for pharmacogenetic testing is a barrier for use in my practice									
2.3 If I wanted to order a pharmacogenetic test, I could identify an appropriate laboratory to perform the testing									
2.4 I have the necessary training to interpret pharmacogenetic testing results									
2.5 I have access to experts that can assist me in interpreting/implementing pharmacogenetic testing results									
2.6 It takes too long to get pharmacogenetic testing results for it to be clinically useful in my practice									
2.7 Pharmacogenetic testing results would assist me in discussing psychotropic medication options with my patients									
2.8 Clinical practice guidelines for the use of pharmacogenetic testing in children and adolescents would be helpful to me									

	Disagree <----------				**Neither**				**Agree** ---------->
Topic 3. Ethical, Legal and Social Implications for Pharmacogenetic Testing	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

3.1 Pharmacogenetic testing results have the potential to cause harm in children and adolescents									
3.2 The risk and benefits of pharmacogenetic testing must be communicated effectively to children/adolescents and their family, so that consent can be given as fully as possible.									
3.3 Health care providers have an ethical obligation to consider pharmacogenetic testing results if they are available									
3.4 Pharmacogenetic testing results could negatively impact a patient's ability to get or keep health/life/disability insurance									
3.5 Pharmacogenetic testing could lead to stigmatization of certain groups of patients									
3.6 Health care providers who fail to act on pharmacogenetic testing results are liable for related harms to their patients									
3.7 Clear legal guidance is required so that fears of liability do not prevent health care providers from using pharmacogenetic testing									
3.8 Ability to pay for pharmacogenetic testing will increase health care inequalities									

We are interested in mechanisms to deliver education on pharmacogenetics:

Which of the following educational offerings about pharmacogenetic testing would be of interest to you? (select all that apply)

- Grand rounds
- Seminar or lecture
- CME/CE course (in-person)
- CME/CE course (web-based)
- Half-day conference
- All-day conference
- Journal articles
- Other (please specify)
- Not interested

Which of the following would you be interested in learning more about? (select all that apply)

- How to interpret pharmacogenetic test results
- Description of pharmacogenetic information in drug labelling
- Laboratories offering pharmacogenetic testing
- Effect of genetic variation on mechanism of drug action
- Recommendations (if any) for prescribing
- Demographics of populations likely to carry genetic variations
- References (scientific literature)
- Other (please specify)
- None

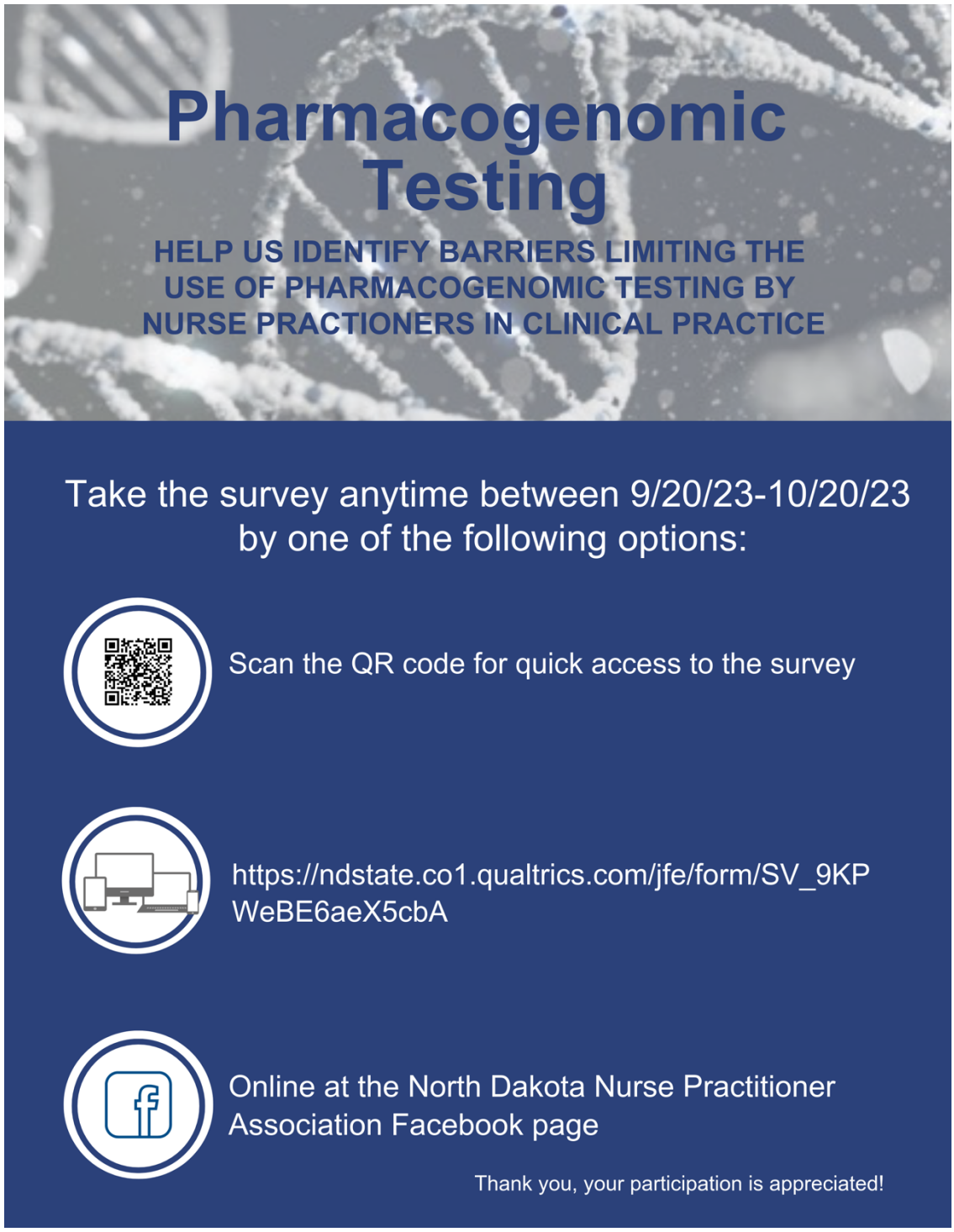
Jessel CD, Maruf AA, Oomen A, Aronld PD, Bousman CA. (2022). Pharmacogenetic testing knowledge and attitudes among pediatric psychiatrist and pediatricians in Alberta, Canada. *Journal of the Canadian Academy of Child and Adolescent Psychiatry,* 31: 18-27.

Please let us know if you have any additional comments regarding the use of pharmacogenetic testing in child and adolescent mental health. (Free text)

Thank you for completing the questionnaire.

A summary of the results will be made available upon completion of the project. If you have any questions regarding this project please feel free to contact Dr. Chad Bousman at chad.bousman@ucalgary.ca

APPENDIX D: QR CODE



APPENDIX E: NDNPA POSTER

NDSU | NURSING

AN ASSESSMENT OF BARRIERS TO NURSE PRACTITIONERS' UTILIZING PHARMACOGENETIC TESTING FOR DEPRESSION

Sierra Entzel, BSN, RN, DNP-Student[1], Carrie Nelson DNP, APRN, FNP-C[1], Allison Peltier, DNP, FNP-C[1], Natasha Petry PharmD, MPH, BCACP[2,3,5], and Kristine Steffen, PharmD, PhD[2,3,4]
North Dakota State University School of Nursing[1], North Dakota State University School of Pharmacy[2], Sanford Health[3], Sanford Center for Bio-behavioral Research[4] Sanford Health Imagenetics[5]

INTRODUCTION

PROBLEM:

- Current depression treatment is trial-and-error approach
- Pharmacogenomic testing is not routinely ordered prior to initiating treatment for depression
- Medications to treat depression can take several weeks to reach therapeutic levels after each adjustment and often require slow dose titrations.
- Genetic testing can determine the rate of drug metabolism within an individual based on the genotype-phenotype relationship.
- CYP enzymes are responsible for the hepatic metabolism of about 75% of all drugs
- CYP2C19 and CYP2D6 antidepressant treatment response

PURPOSE:

- To determine barriers that hinder the use of Pharmacogenomic testing to guide treatment for individuals diagnosed with depression despite known benefits.

CPIC Clinical Pharmacogenetics Implementation Consortium
KNMP
PHARMGKB
U.S. FOOD & DRUG ADMINISTRATION

11% U.S. Population taking an antidepressant — Alemi et. al 2021

21 MILLION # of U.S. adults that have had at least one depressive episode — NSDUH, NIH

60% % of depressed patients that do not benefit from first antidepressant prescribed — Lake & Turner 2017

10 YEARS Average length of time to obtain treatment after initial depressive symptoms begin
- *>2/3 of those patients never receive adequate care*

Lake & Turner, 2017

$31 BILLION Estimated loss in productivity related to unmet treatment needs of depression — Lake & Turner, 2017

Genomics Used to Improve DEpression Decision (GUIDED) trial

1398 adult participants over a 24-week period
2 Groups: Treatment as Usual (TAU) and Pharmacogenomic guided treatment (PGT)
After 8 weeks – PGT participants vs. TAU had
- Symptom improvement (p=0.036)
- improved treatment response (p=0.002)
- higher rates of remission (p=0.066)

PROJECT OBJECTIVES

- Identify current rates of utilization of pharmacogenomic testing amongst Nurse Practitioners responsible for the treatment of depression.
- To determine barriers to nurse practitioners utilizing pharmacogenetic testing for prescribing psychotropic medications used to treat depression.
- Assess NPs beliefs regarding pharmacogenomic testing

PROJECT DESIGN

Project Type: Practice improvement project through needs assessment
Sample: Nurse practitioners
Method:
- Self-paced survey open for 10-day period.

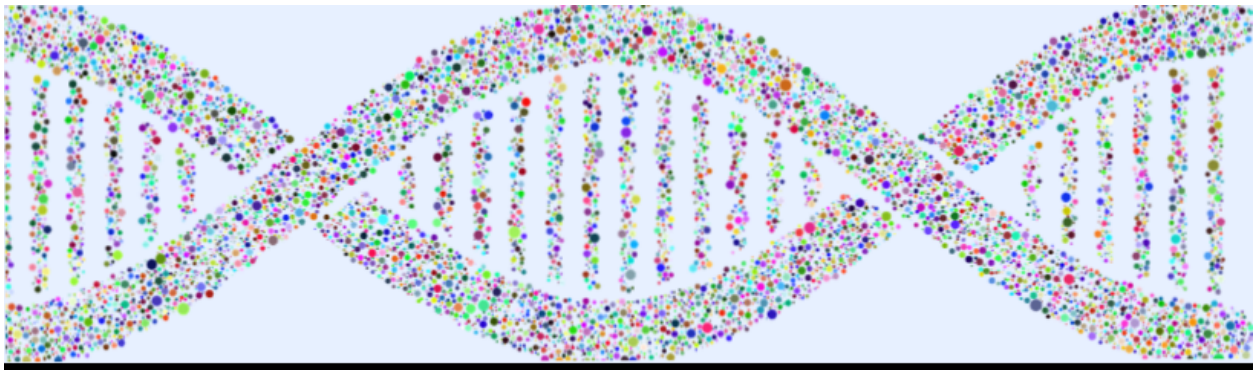
Evaluation:
- Qualitative data collected via online survey through Qualtrics.
- Survey assesses demographics, knowledge, comfort, ordering testing, guidelines, personal beliefs, and barriers that limit the use of PGT within clinical practice.

Summary/Results: Currently pending

RESOURCES

Available upon request

APPENDIX F: EXECUTIVE SUMMARY



EXECUTIVE SUMMARY:
BARRIERS OF PHARMACOGENOMIC TESTING TO GUIDE DEPRESSION TREATMENT

DEPRESSION

- Leading cause of disability worldwide according to the World Health Organization (WHO, 2021).
- Affects all ages and can be life threatening if left untreated.
- Current medication treatment is trial-and-error approach requiring strict treatment adherence and time to reach therapeutic drug levels.
- 60% of patients do no benefit from first medication prescribed (Alemi et al., 2021).

PHARMACOGENOMIC TESTING (PGT)

- Can determine the rate of drug metabolism within an individual based on the genotype-phenotype relationship.
- CYP enzymes account for 75% of hepatic clearance, with CYP2C19 and CYP2D6 determining how individuals respond to antidepressant treatments.
- Uptake to utilizing PGT to guide depression treatment remains slow, despite known benefits.

PROJECT

- Self-paced online survey dispersed to NPs at 15th annual NDNPA conference and via NDNPA Facebook
- Total sample size: 23
- NP licensure in North Dakota, Minnesota, South Dakota, and Nebraska

RECOMMENDATIONS FOR PRACTICE

- Incorporate PGT into education curriculum and include: implications for use, interpreting results, available resources, collaboration with pharmacists, insights into providing patient education, cost and benefits of PGT.
- Improve confidence in utilization of PGT into routine practice by furthering provider education.

RESULTS

Total Sample Size = 23

87%

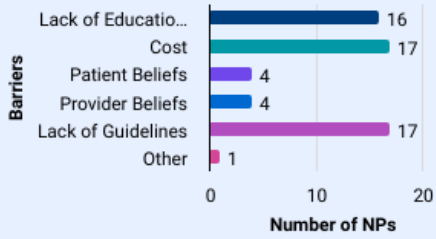
NPs that reported they believed PGT can improve outcomes in individuals diagnosed with depression

57%

57% of NPs surveyed have ordered PGT

- 76% of those have ordered PGT to treat depression

Barriers Hindering the Utilization of PGT to Guide Treatment for Depression



87% of NPs reported having formal education surrounding pharmacogenomics. Only **52%** reported their formal education included incorporating PGT to manage depression treatment

When asked about how confident participants would feel ordering PGT to guide depression treatment, **26%** reported feeling "somewhat" confident while **26%** "strongly disagree" that they would feel confident. **35%** reported feeling neutral.

Education Opportunities for Providers:

- National Human Genome Research Institute
  https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Guidelines

Available Guidelines:

- Clinical Pharmacogenomics Implementation Consortium (CPIC) Guidelines
  - https://cpicpgx.org/guidelines/
- Dutch Pharmacogenetics Working Group
  - https://www.knmp.nl/
- Pharmacogenomics Knowledge Base (PharmGKB)
  - https://www.pharmgkb.org/
- Flockhart Table
  - https://drug-interactions.medicine.iu.edu/
- Food and Drug Administration (FDA)
  - Table of Pharmacogenetic Associations | FDA