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Depression Outcomes in Care Coordination, Primary Care and Psychiatry Patients After Pharmacogenetic Testing

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DEPRESSION OUTCOMES IN CARE COORDINATION, PRIMARY CARE AND PSYCHIATRY PATIENTS AFTER PHARMACOGENETIC TESTING

BY

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This dissertation is approved as a creditable and independent investigation by a candidate for the Doctor of Philosophy degree and is acceptable for meeting the dissertation requirements for this degree. Acceptance of this dissertation does not imply that the conclusions reached by the candidate are necessarily the conclusions of the major department.

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I would like to dedicate this dissertation to my family.

First, my husband, Steve Kittelsrud, who "bet" that I would end up getting my PhD, when I said that I wasn't going to, and then encouraged and supported me to its completion. I love you with all my heart.

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ABBREVIATIONS

1. Chronic Disease Self-Management Program (CDSMP)
2. Patient activation measure-13 (PAM-13)
3. Body Mass Index (BMI)
4. Body pain (BP)
5. Care coordination primary study nickname (PGX-TIME)
6. Chronic Illness Care Model (CICM)
7. Clinical Pharmacogenetic Implementation Consortium (CPIC)
8. Colorado symptoms Instrument (CSI)
9. Comprehensive Major Medical (CMM)
10. Consumer-driven Health Plan (CDHP)
11. Cytochrome P450 enzyme pathway (CYP)
12. Cytochrome P450, family 1, subfamily A, polypeptide 2 (CYP 1A2)
13. Cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP 2C19)
14. Cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP 2D6)
15. Cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP 3A4)
16. Depression disorder- not otherwise specified (DDNOS)
17. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)
18. Dorothea Orem's Self-Care Deficit Theory (SCDT)
19. Drug-Drug Interaction (DDI)
20. Drug-Drug-Gene Interaction (DDGI)

21. Drug-Gene Interaction (DGI)
22. Dutch Pharmacogenetic Working group (DPGW)
23. Food and Drug Administration (FDA)
24. General health (GH)
25. Health Reimbursement Arrangement (HRA)
26. Hemoglobin A1C (HgA1C)
27. Low-density lipoprotein (LDL)
28. Major depressive disorder (MDD)
29. Mental composite score (MCS)
30. Mental health (MH)
31. Morisky Medication Adherence Scale (MMAS-8)
32. National Institute of Mental Health (NIMH)
33. Patient activation measure (PAM)
34. Patient Activation Measure- Mental Health (PAM-MH)
35. Patient Health Questionnaire (PHQ-9)
36. Pharmacogenetic Research Network (PGRN)
37. Pharmacogenetics (PGX)
38. Pharmacogenetics report (PGXr)
39. Physical component scores (PCS)
40. Physical functioning (PF)
41. Role emotional (RE)
42. Role physical (RP)

43. Selective Serotonin Receptor Inhibitor (SSRI)
44. Self-Care Deficit Theory (SCDT)
45. Self-Management survey (SM)
46. Sequenced Treatment Alternative to Relieve Depression (STAR*D)
47. Serious mental illness (SMI)
48. Short Form Quality of Life (SF-12)
49. Short Form Quality of Life (SF-36)
50. Social functioning (SF)
51. The Quick Inventory for Depressive Symptoms- Self Report (QIDS-SR16)

    United States (US)
52. Ultra-Rapid (UR)
53. Vitality (VT)

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ABSTRACT

PATIENT ACTIVATION AND MEDICATION ADHERENCE AFTER PHARMACOGENETIC CARE IN A CARE COORDINATION POPULATION

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Objective. The purpose of the study is to compare the outcomes of patient activation before and after pharmacogenetic care in a coordinated care population. The process of pharmacogenetic care includes the patient's acknowledgment of medication changes which are based on their genetic profile. This study will be framed by Dorothea Orem's Self-Care Theory and Davies and Conley's framework of genetic influences in prescribing anti psychotropic therapy.

Background. Understanding patient's behavioral reactions to pharmacogenetic care in terms of patient activation is important to understanding patient's health outcomes. No published studies were identified in literature reviews conducted by this author which related to patient activation and pharmacogenetic care. There were no published studies found by the author using either, or both of, Dorothea Orem's Self-Care Theory or Davies and Conley's framework.

Methods. This dissertation study is designed as part of a larger study nicknamed "PGX-TIME". The study is a longitudinal, utilizing one-group, repeated measure design. Participants will complete the Patient Activation Measure-Mental health (PAM-MH) before and after having pharmacogenetic testing (PGX). Medication recommendations will be provided to the primary care provider based on current medications and genetic

testing results. Standard of care in South Dakota requires patient involvement and communications regarding genetic testing. This study requires a patient's acknowledgment that their medications are remaining the same or being modified based on pharmacogenetic testing results. Additional information will be collected regarding the number of chronic conditions, the number of mental health conditions, the number of medications utilized, coordinated care tier level and number of genetic pathways affected. A theoretical model was developed based on literature review, Orem's model, Davies and Conley's framework, to understand direct and indirect variable relationships.

Results. This study was stopped in January of 2016. Therefore, no study results are presented in this dissertation. Chapter one and two describe this study while chapter three describes the reason the study was stopped and how the study changed. Chapter four presents study results, and Chapter Five includes the discussion.

CHAPTER 1

Introduction

Phenomenon of Interest

Mental illness is a common and significant co-morbid condition to other health-related problems such as diabetes (Trief et al., 2014), cardiovascular disease (Sin, Yaffe, & Whooley, 2015), and obesity (Stanley, Laugharne, Addis, & Sherwood, 2013). The combination of chronic disease associated with mental health diagnoses cost the U.S. healthcare system over $300 billion dollars in 2002, and about $210 billion of this is related to work absenteeism costs due to worker impairment. Reeves et. al. (2011) found that in South Dakota approximately three days per month are used for mental health days indicating loss of work time (Reeves et al., 2011). Many studies have evaluated the best way to care for patients with depression through primary care and psychiatric care including a more recent large-scale study titled the Sequenced Treatment Alternatives to Relieve Depression (Ben-Zeev et al., 2012; Smith, Easter, Pollock, Pope, & Wisdom, 2013; Steigman et al., 2014; Tosh, Clifton, Xia, & White, 2014; Wisniewski et al., 2004)

Patient activation is one's knowledge, skills and ability to navigate the health care system (Hibbard, Sockard, Mahoney, & Tusler, 2004). Patient activation is also closely related to health outcomes in persons with chronic illness and mental health diagnoses, and authors report that those who have higher activation levels have improved mental health outcomes even a year later (Sacks, Greene, Hibbard, & Overton, 2014). Another measure of patient activation is medication adherence (Hibbard, et al., 2004).

Evidence has demonstrated that medication adherence in chronic mental illness is poor and that medication non-adherence increases the incidence of re-hospitalization along with worsening patient outcomes (Mosen et al., 2007; Remmers et al., 2009). Medication management of mental illness most often includes more than one medication over long periods of time (Blaschke, Osterberg, Vrijens, & Urquhart, 2012). A German study by Stieffenhofer and Hiemke (2010) indicated that medication side effects, which occur because of personal enzymatic pathways associated with one's genetic make-up, may play a role in discontinuation of medications. Hall-Flavin et al. (2013) note that pharmacogenetic guidance in medication selection reduced symptoms and improved clinical outcomes for patients. Pharmacogenomics (PGX) is the study of genetics as they relate to the cytochrome P450 (CYP) enzymatic metabolism of medications in the liver (Zhou, Liu, & Chowbay, 2009). Pharmacogenetic testing in recent years has been reported to decrease side effects which may contribute to reducing medication non-adherence (Hall-Flavin et al., 2013; Mrazek, 2010b). Currently, there are no identified published studies that evaluate the effect pharmacogenetic testing has on patient activation, and one published study related to medication adherence (Fagerness et al., 2014). There is a growing body of evidence regarding improvement of patient outcomes related to positive changes in patient activation (Sacks, et al., 2014; Sacks, Greene, Hibbard, Overton, 2014)(R. M. Sacks, J. Greene, J. H. Hibbard, & V. Overton, 2014). Additionally, studies address the potential of pharmacogenetic testing to impact medication adherence because of the reduction of side effects (Hall-Flavin et al., 2013; Hall-Flavin et al., 2012). It is the intent of this study to evaluate patient activation

before and after pharmacogenetic testing has been performed to confirm or adjust patient medications.

Background

Few published research studies have focused on the effect genetic testing, such as pharmacogenetic testing, has on patient behavior (Sacks et al., 2014; Sacks et al, 2014) patient behavior. The process of conducting genetic testing requires a specific process be followed in South Dakota, and standard of care requires open communications between providers and patients. As the standard of care, the provider will discuss the testing and any medication changes based on the pharmacogenetic testing results with the patient's acknowledgment of the process (Appendix A). This process will be considered pharmacogenetic care for this study.

There are currently no published studies identified at this time, which examine patient activation and pharmacogenetic care. Patient activation improves not only medication adherence but also health outcomes. When a patient is activated or engaged in their healthcare, there is increased motivation in health-related behaviors. Some of these include; improved diet, exercise and obtaining preventative screening tests (Hibbard et al., 2004). Several studies have reported that high patient activation measures correlate to better health outcomes in biometric indicators of health such as blood pressures, Hemoglobin A1C (HgA1C) levels, cholesterol levels, and body mass index (Hibbard & Greene, 2013; Rogvi, Tapager, Almdal, Schiotz, & Willaing, 2012; R. Sacks et al., 2014; Skolasky, Mackenzie, Wegener, & Riley, 2011).

A component of the measurement of patient activation is the outcome of medication adherence. Haga and LaPointe (2013) have speculated that the act of

pharmacogenetic testing will increase a patient's medication adherence. However, only one published study was identified by Fagerness et al. (2014) which examined pharmacy refill data for those patients who received pharmacogenetic testing. This study reported higher medication adherence in those patients who had genetic testing over those who did not have testing. Furthermore, Haga and LaPointe (2013) described additional factors that may relate to other positive impacts of pharmacogenetic testing, such as less need for medication dosing adjustments, fewer changes in medications, fewer side effects, opening communication between provider, and patient and the potential of less time to therapeutic outcomes. These factors may contribute to medication adherence after pharmacogenetic testing and, therefore, increase patient activation.

Some studies have addressed improved medication adherence in patients who have had genetic risk testing (Charland et al., 2014; Grant et al., 2009). Grant et al. (2009) reported that participants with and without type 2 diabetes indicated in a self-report survey that they would be more likely to have higher motivation to change their lifestyle if they had a 'high risk' gene for diabetes. Moreover, participants described that they would be 'much more motivated' to be compliant with their medications (Grant et al., 2009). Additionally, Charland et al. (2014) reports increased adherence to statin medications after testing the risk gene, KIF6, which indicates increased risk for Congestive Heart Disease (CHD). One recent study evaluating retrospective health claims refill data, noted that those participants who had pharmacogenetic testing were more adherent to their medication (Fagerness et al., 2014).

Patient activation has been noted to be low in patients with mental health disorders (Gunn et al., 2012; R. Sacks et al., 2014; Whooley et al., 2008). As defined by

Hibbard (2008) activation refers to how engaged one is in managing his or her healthcare and this can change over time. It follows that if pharmacogenetics may improve a patient's engagement in their healthcare, medication adherence may also improve. The amount of activation a patient may have in his or her healthcare is variable based on patient interest, skills, the capacity to understand and diagnoses (Von Korff, Gruman, Schaefer, Curry, & Wagner, 1997). To date, there were no studies identified in this author's literature review which examined the patient response to pharmacogenetic testing as a relationship to patient activation.

Problem statement

Pharmacogenetics is an innovation that is becoming more widely accepted as a clinical application of genetics, and its implementation has shown benefit with psychiatric medications in mental health (Hall-Flavin et al., 2013; Mrazek, 2010a; Mrazek & Lerman, 2011). Within the context of clinical implementation, pharmacogenetic (PGX) testing may have indirect effects that may benefit patient behavior, such as increasing medication adherence (Charland et al., 2014). It follows that if there is evidence of increasing medication adherence, there could also be an increase in patient activation. However, a study utilizing patient activation has not been conducted in mental health and chronic illness population in association with medication adjustments based on pharmacogenetic testing.

Purpose of the Study

The purpose of the study was to compare the outcome of patient activation before and after medication recommendations have been made utilizing pharmacogenetic testing information in a chronic illness and mental health population.

Care coordination patients had access to pharmacogenetic care. Based on pharmacogenetic testing and a pharmacist's review of current medications, recommendations for medication and or dosage adjustments were made. The provider was assigned to oversee the patient along with the care coordinator who provided the information to the patient regarding their completed pharmacogenomic testing results. Also, the coordinator and or the provider communicated that their medications were being adjusted based on the genetic test. The patient acknowledged that their medication is being changed or not changed based their personal genetic profile. Other variables that were collected for a primary study (PGX-TIME) were also incorporated into the analysis for the dissertation such as, demographic information, number of CYP enzyme pathways that are clinically affected by decreased or increased enzyme activity, number of chronic conditions, the number of prescription medications and the number of mental health conditions.

Research Questions and Hypotheses

1. Does patient activation improve from admission to one month of care coordination in a population of patients with chronic conditions and mental illness?
    a. Patients with chronic conditions and mental health will improve patient activation scores after beginning care coordination.
    b. $H_0 = PA_{T1} = PA_{T2}$
    c. $H1 = PA_{T1} < PA_{T2}$

2. Does patient activation improve after pharmacogenetic care in patients with chronic illness and mental health diagnoses who are participating in a care coordination population?
    a. Patient activation scores will improve from time 2 to time 3 after pharmacogenetic care.
    b. $H_0 = PA_{T2} = PA_{T3}$
    c. $H_1 = PA_{t2} < PA_{t3}$
3. Does patient activation improve after patients with chronic illness and mental health enter care coordination and have pharmacogenetic care?
    a. Patient activation scores will improve from time 1 to time 3 after entry to care coordination and pharmacogenetic care.
    b. $H_0 = PA_{T1} = PA_{T3}$
    c. $H_1 = PA_{T1} < PA_{T3}$
4. Do the classifications of TIER level, number of medications, number of chronic illnesses, and number of affected genes, affect the level of change in patient activation in a care coordination population?

Nursing Theory

Dorothea Orem's Theory of Self-Care Deficit includes three midrange theories, which together attempt to define nursing practice and guide nursing curriculum (Orem, 2001). The three theories include; Theory of Self-Care, Theory of Self-Care Deficit, and Theory of Nursing Systems (Orem, 2001; Parker & Smith, 2010). This study will incorporate the Theory of Self-Care as measured by the PAM-MH and MMAS-8.

Three central concepts including; "self-care, self-care agency and therapeutic self-care demand" make up self-care theory (Denyes, Orem, & Bekel, 2001; Nursing Development Conference Group, 1979; Orem, 1987, p. 70) Self-Care is a learned, voluntary and deliberate activity to maintain wellness and health (Nursing Development Conference Group, 1979; Orem, Taylor, & Renpenning, 1995). Patient activation (PAM-MH) is evidence of self-care in its measures of self-capability, learned knowledge and beliefs of health care and medication use (Green et al., 2010; Hibbard et al., 2004). Additionally, medication adherence, as measured by the MMAS-8, is evidence of self-care and self-care requisites (Morisky, Ang, Krousel-Wood, & Ward, 2008).

Self-care agency is the power and ability to care for the self, and, therefore, nursing agency is the capability, knowledge and insight into the patients needs as self-care agents with deficits (Renpenning & Taylor, 2003). Motivation and motives are the basis for self-care agency and are followed by the health behavior actions. This study evaluated self-care agency as a component of patient activation, and medication adherence as a part of self-care requisites.

Theoretical Framework

Davies, Conley and Puskar (2010) produced a theoretical framework targeted to the practicing clinician. It was developed by evaluating challenges that clinicians face when choosing antipsychotic medications. The challenges are that a provider must be aware of, and knowledgeable regarding pharmacology of drugs, molecular genetics of drug targets, and genetics of drug metabolism to prescribe medications (Davies, Conley, & Puskar, 2010). Components of the framework related to patients include; family and

patient education, medication planning, medication monitoring, and patient outcomes (Davies et al., 2010).

Definition of terms

Mental health. Mental health conditions most commonly seen by the care coordination team includes, depression, anxiety, personality disorders, post-traumatic-stress disorder, bipolar-disease, and schizophrenia. However, this list may vary based on the population of the primary study, PGX-TIME.

Serious Mental Illness (SMI). SMI is when mental health disorders are serious enough to impact a patient's activities of daily living (NIMH, 2012). The population for this study has mental health conditions in the category of serious mental illness.

Patient Activation. An activated patient is a patient who has the knowledge, skills and ability to navigate the health care system to engage in personal self-care to maintain health and wellbeing (Hibbard et al., 2004).

Medication Adherence. Medication adherence is the ability and willingness to take medications as they are prescribed by a provider on a continuing basis to maintain health (Morisky et al., 2008; Morisky & DiMatteo, 2011).

Pharmacogenetics. Pharmacogenetics (PGX) is the study of genetics as they are related to the cytochrome P450 (CYP) enzymatic metabolism of medications, transporter and receptor genes in the liver (Zhou et al., 2009).

Pharmacogenetic care. Pharmacogenetic care refers to the provider and patient interaction that surrounds the process of testing. These elements include the patient's informed consent to perform the genetic testing, a provider order, a return of genetic

report with information regarding pharmacist recommendations and the patient's acknowledgment that medication changes were made based on their genetic profile.

Significance of the Study

This study is significant to patient outcomes, providers, and health systems. Patients who have pharmacogenetic testing and show an improvement in patient activation will have better health outcomes such as improved mental health conditions, decreased depression, decreases in symptoms and side effects and overall, improved quality of life. Potentially, there may be a benefit to both the patient and insurance providers related to costs. For example, when one is started on the correct medication because the provider understands not only the clinical picture but also the genetic snapshot of a patient's drug metabolism, the patient will have improvement in their health conditions. Moreover, the patient may experience fewer side effects without the expense of frequent changes in medications or additional medications to control these side effects.

In consideration of providers and other professions working with patients, opening communication between the provider and patient because of pharmacogenetic testing may increase patient activation and medication adherence. Furthermore, increases in activation and medication adherence may decrease the number of suicides, promote patient's active participation in preventative medicine, decrease missed clinic visits and promote the intentional and appropriate use of resources. This study is a broad-reaching study when considering the potential impact on patient's health outcomes, costs to the patient and hospital systems, and availability of new prescribing resources for the provider in an ever-changing and complex system of pharmaceuticals.

CHAPTER 2

Literature review

Introduction

Chapter two reviews the current literature as it relates to the primary points of interest to this study. This study compared the outcome of patient activation before and after medication recommendations had been made utilizing pharmacogenetic testing in a chronic illness and mental health population. Therefore, current literature related to the following topics was critically evaluated; (a) prevalence and trends in mental health care; (b) patient activation, the concept itself and its relationship to chronic illness, diabetes, hypertension, and mental health; (c) medication adherence; (d) pharmacogenetics and behavioral outcomes; and (e) gaps in the literature related to pharmacogenetics and behavioral outcomes in the mental health population.

Prevalence and Trends in Mental Health

Serious mental illness (SMI) as defined by the National Institute of Mental Health (NIMH), as a diagnosis of mental illness in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) seriously impacts a patient's daily life (NIMH, 2012). SMI accounts for 9.4 million people in the United States (US) alone, which is about 4.1 percent of the US population (NIMH, 2012). The gender most affected with SMI are females (4.9 %), and the age ranges between 26-49 years old (5.2%) (NIMH, 2012). Also, Medicaid use within this population is significant at about 8.5% of patients with SMI (NIMH, 2012). Many patients with SMI do not seek out mental health services. However, a survey in 2008 reports that 40% of patients with mental health conditions first utilize primary care (Center for Disease Control, 2008).

Significant physical conditions are associated with mental illness and include diabetes (Trief et al., 2014), cardiovascular disease (Sin et al., 2015), and obesity (Stanley et al., 2013). The combination of mental illness and chronic conditions affect the ability of patients to care for themselves. Additionally, poor outcomes, such as increased depression, and increased suicide are associated with this combination of disorders (Salyers, Matthias, Sidenbender, & Green, 2013; Trief et al., 2014).

There are many issues leading to under-recognition and insufficient treatment of psychiatric illness in the primary care setting (Eisenberg, 1992; Gallo & Coyne, 2000; Williams, 1998). One such issue is a general reluctance due to stigma, of patients to report mental illnesses and instead, patients seek primary care services for somatic complaints (Wells et al., 2000; Williams, 1998). The ability to seek appropriate care, as part of patient activation, is an important step in self-care management (Chen, Mortensen, & Bloodworth, 2014; Orem, 2001). Katon et al. (1997) estimate that as high as 80% of patients with depression seek out primary care services for somatic complaints without mention of depressive symptoms to the primary provider. Another issue is finding the correct treatment for the patient. In the 1990's the Food and Drug Administration (FDA) approved Selective Serotonin Receptor Inhibitors (SSRI's), which increased the number of prescriptions through primary care services. This increase was related to the decreased risk of side effects and the decreased need for follow-up (Cutler, 2001; Cutler & McClellan, 2001).

Paton, Esop, Young, and Taylor (2004) conducted a clinic review of recorded lipids and Body Mass Index (BMI) in schizophrenic patient charts, and reported that these data were not found in the majority of schizophrenic patient charts reviewed.

Similarly, Roberts, Roalfe, Wilson, and Lester (2007) examined charts of schizophrenia patients who use primary care and found that an inequality of care exists compared to other patients reporting that schizophrenia patients were half as likely to have blood pressure and cholesterol levels checked than asthma patients. However, Tosh et al. (2014) completed an extensive review of the literature and revealed that overall the literature does not report clear inequalities between schizophrenia patients and other patients. There is inconclusive, yet potentially negative evidence, in the literature review regarding the quality of care, and access to care that patients with mental health conditions experience.

Muir-Cochran (2006) report that patients with mental health conditions have increased challenges with negotiating the medical system and therefore, are less activated in their health care. It is documented that patients with mental illness are less engaged in their health care than those without mental illness (Muir-Cochrane, 2006). Overall, the high prevalence of complicated patients with mental health disorders who are being cared for in primary practice illustrates a clear picture of the unmet needs of this population.

Patient Activation Literature Review

The literature was searched using the keyword in quotations, "patient activation", which yielded 944 articles on EBSCOhost choosing all databases. Limiting the scope to the full article, and peer-reviewed articles, a total of 342 articles were available. When the scope was narrowed to "patient activation" and "chronic illness", 144 articles were noted as available. These abstracts were reviewed for relevance to the study. Articles were also obtained from the PAM website www.insigniahealth.com to total 71 articles evaluating patient activation in various chronic disease states. A discussion of the

concept development related to patient activation and a review of literature related to chronic conditions follows.

Patient Activation

The socially driven underpinnings of the concept of "patient activation" are directed at two main health initiatives. The first is the transition of reimbursement towards patient-centered containment of costs with improving health outcomes or consumer-driven insurance plans (Hibbard et al., 2004). The second is Bodenheimer, Lorig, Holman, and Grumbach (2002) development of the Chronic Illness Care Model (Hibbard et al., 2004).

Health plan impact. Consumer-driven health plans (CDHP) was a cutting-edge topic debated at the 6th Annual World Health Care Congress in 2009 ("Making the Shift to Consumer-Directed Health Care Remains a Challenge for Many," 2009). At the heart of the discussions were issues related to empowerment of the patient to become engaged in their health plan by allowing incentives from insurance companies ("Making the Shift to Consumer-Directed Health Care Remains a Challenge for Many," 2009). The term "consumer-driven" is a reference to the design of insurance reimbursement programs that puts the patient at the center of the decision process for their personal care (Gabel, Lo Sasso, & Rice, 2002, p. W395).

A study conducted by Loeppke et al. (2008) evaluated a health enhancement program following a risk assessment on employees' health. The health enhancement program encouraged participants to make healthy choices and participants were able to earn $300 off of their insurance premiums. The next year of health screenings showed an improvement in health outcomes (Loeppke et al., 2008). Similarly, HRA plan members,

who engaged in better health practices reportedly used less asthma, cardiac, and cholesterol medications (Song, Levin, & Gartner, 2010). Wilson et al. (2008) researched utilization differences between those enrolled in a CDHP and a comprehensive major medical (CMM) plan. The findings show no differences in utilization of services in the areas that were beyond the patient's control such as inpatient hospital stays. However, there was a significant reduction in the use of preventative services and emergency room visits for those with CDHP's (Wilson et al., 2008). An evaluation of CDHP members reported that they followed healthier self-care behaviors than non-memebers. For example, fewer members engaged in smoking, more members exercised, and more obtained preventative exams (Fronstin, 2012). This example illustrates that a high engagement in one's self-care behaviors reportedly improves health outcomes.

Chronic illness care model impact. Edward H Wagner, MD developed the Chronic Illness Care Model (CICM) which is based on six elements that when incorporated by the patient and primary provider increase the collaboration and effectiveness of the healthcare system (Bodenheimer, Wagner, & Grumbach, 2002). These six pillars are similar to the philosophical underpinnings of patient activation and include; support of self-management, clinical information structure, redesign of the delivery system, decisional support, health care organization, and community resources (Bodenheimer, Wagner, et al., 2002).

Philosophical underpinnings of Patient Activation. Hibbard et al. (2004) conducted focus groups to understand and conceptualize "activation" and conducted a literature review, searching terms related to the concept. This review identified six domains which were utilized in focus groups and include; (a) self-management of

symptoms; (b) engagement in health maintenance activities; (c) conduct activities that maintain health; (d) participation in treatment decisions; (e) work with caregivers and providers; (f) understand the health system operations and ability to navigate the system (Hibbard et al., 2004). These six findings directed the focus group discussions.

An expert panel and patient panel were queried regarding patient's *"knowledge, beliefs, and skill needed to manage and live with a chronic condition"* as they relate to each of the six identified areas found in the literature (Hibbard et al., 2004, p. 1008). The expert panel identified that the patient is important in the areas of self-management, collaborating with the provider, and maintaining function. Additionally, they concluded that knowledge and skills are needed to self-manage, and maintain functional health. Alternatively, they described that knowledge was not needed for collaboration with a provider, but skills were valuable in collaborating with a provider (Hibbard et al., 2004). Overall, activated patients believe in, and know how to, self-manage their chronic conditions use their collaborative skills and have the ability to navigate the system.

Patient activation and disease states. Five studies identified, have provided evidence that highly activated patients have better health behaviors such as, being exercisers, non-smokers, and those who follow-up with preventative exams (Hibbard, Mahoney, Stockard, & Tusler, 2005; Hibbard et al., 2004; Hibbard, Mahoney, Stock, & Tusler, 2007). Overall, patient activation has been evaluated in many settings, and health states representing chronic illness (Alexander, Hearld, Mittler, & Harvey, 2012; Kinney, Lemon, Person, Pagoto, & Saczynski, 2015), diabetes (Begum, Donald, Ozolins, & Dower, 2011; Rask et al., 2009; Woodard, Landrum, Amspoker, Ramsey, & Naik, 2014), hypertension (Ryvicker, Feldman, Chiu, & Gerber, 2013; Thiboutot et al., 2013),

orthopedic surgery (Skolasky, Mackenzie, Wegener, & Riley, 2008), heart failure (Gardetto, 2014; Shively et al., 2013), Inflammatory bowel disease (Munson, Wallston, Dittus, Speroff, & Roumie, 2009), and multiple sclerosis (Goodworth et al., 2014; Packer et al., 2015; Stepleman et al., 2010).

Patient activation and chronic illness. Provider contact and communication contributes to higher activation levels and is exemplified by the information that patients with higher activation levels perceive a good relationship with their providers and see that their treatment plans were fairly executed (Alexander et al., 2012). Additionally, Wong, Peterson, and Black (2011) found that the more time spent with a provider, the higher the activation level became. Overall, diabetic and cardiovascular disease patients with higher activation decreased the number of visits to their provider, potentially indicating better self-management (Donald et al., 2011).

Information on patient activation and patient outcomes are new and rapidly growing with 27 articles published since 2007 relating to patient outcomes as they relate to patient activation levels. It is important to understand how having a high, or low activation level relates to patient outcomes. For example, those with low activation levels were found to have a higher risk for re-hospitalization and risk for higher numbers of emergency room visits (Kinney et al., 2015). When Remmers et al. (2009) conducted a secondary analysis on data collected for a previous study by Mosen et al. (2007) and collected additional information for each participant, they found that patient activation is a malleable trait that declines over time. These authors suggested that this change is due to a decreases in perceived health, and a reduction in ability to care for themselves (Remmers et al., 2009). When health outcomes were assessed in the four areas of

prevention, unhealthy behaviors, clinical indicators and costly utilization, it was found that those with high activation had fewer emergency room visits and lower systolic blood pressure. However when comparing those with high activation to those with lower activation levels, triglycerides, Low-Density Lipoprotein (LDL), HgA1C levels and diastolic blood pressures did not differ (Greene & Hibbard, 2012). Also, patients who have low patient activation along with multiple chronic illnesses who participate in care coordination tended to self-report problems with care coordination (Maeng, Martsolf, Scanlon, & Christianson, 2012).

Patient activation and diabetes. Chronic conditions like diabetes require daily monitoring plus the skill and knowledge to self-manage (Rask et al., 2009; Remmers et al., 2009). Patient activation on the topic of diabetes care evaluated the health outcomes of self-management, and associations with HgA1C. Rask et al. (2009) studied 287 African Americans, who were primarily female and uninsured, finding that those more activated patients performed frequent foot exams, had eye exams annually, and higher self-management skills. However, there was no evidence that patient activation had any relationship to HgA1C levels (Rask et al., 2009). On the other hand, Remmers et al. (2009) reflected that those who had higher PAM levels had lower HgA1C levels and decreased LDL levels. Moreover, the converse was true as well, indicating a predictive nature of the PAM to health outcome measures of HgA1C (Rask et al., 2009). In contrast, Mayberry et al. (2010) concluded that only those with the highest level of activation as scored by the PAM would see a decrease in HgA1C levels. These studies indicate that patient activation has an impact on diabetes self-care, but that there may be

other issues influencing HgA1C levels that are more complex than what patient activation may measure.

Intervention studies have indicated that there are several methods to improve activation and, therefore, diabetes self-care behaviors and outcomes. Bolen et al. (2014) reviewed the literature and conducted a meta-analysis illustrating the effectiveness though mild, of patient activation interventions. Social support and participatory decision making as interventions were positively related to higher patient activation scores on the PAM and better HgA1C levels (Parchman, Zeber, & Palmer, 2010; Schiotz, Bogelund, Almdal, Jensen, & Willaing, 2012). It has been previously shown that by improving activation levels, patient health outcomes and costs improve (Greene, Hibbard, Sacks, Overton, & Parrotta, 2015). Additionally, online interventions and educational programs have been reported as effective to improve diabetes-related outcomes and patient activation (Lorig, 1996; Lorig et al., 2010).

Patient activation and hypertension. A study using interventions to improve patient activation in a primarily black, hypertensive population, did not show positive outcomes for the intervention but concluded that those with low activation improved control better than those with higher activation scores (Ryvicker et al., 2013). In the study by Ryvicker et. al. (2013), it was reported that those participants who had higher activation levels, were younger aged, had lower blood pressures, higher health literacy, higher education levels, fewer medications, and diabetes. Other studies also have had difficulty finding patient activation interventions to be successful in reducing blood pressures, having similar findings to the study by Ryvicker et al. (2013) with patient activation (Thiboutot et al., 2013; Wagner et al., 2012).

Patient activation and other illnesses. Other diagnoses, such as heart failure (Gardetto, 2014; Shively et al., 2013), inflammatory bowel disease (Munson et al., 2009), multiple sclerosis (Goodworth et al., 2014; Packer et al., 2015; Stepleman et al., 2010) and orthopedic surgery (Skolasky, Mackenzie, Riley, & Wegener, 2009; Skolasky, Maggard, Li, Riley, & Wegener, 2015), have been also been studied in association to patient activation . These conditions may be similar to the population in chronic care coordination who will participate in this study.

Gardetto (2014) evaluated patient activation in patients who had heart failure attempting to link characteristics such as, confidence and emotional status, to activation in those with chronic conditions plus heart failure. This study found a mediating relationship between increased confidence and higher scores of activation, and partial mediation of self-management behaviors (Gardetto, 2014). Those patients who were more activated in their care had better heart failure outcomes, such as improved New York Heart Association scores, functional capacity, and anxiety, than those who were less activated (Gardetto, 2014). Shively et al. (2013) conducted a randomized controlled study of an intervention to improve patient activation in heart failure patients and found similar results to Gardetto (2015). The conclusion in both studies was that those patients who were more activated had better health outcomes with their heart failure management (Gardetto, 2014; Shively et al., 2013).

Patient activation and mental health. The literature searches for patient activation and mental health turned up one article for PAM-MH, related to the tool development. Subsequent searches revealed that mental health conditions tended to be

included under the general term of "patient activation" and overall 14 studies were evaluated which were identified on a reference list from www.insignia.com.

Patients with mental illness are noted to have reduced motivations to seek medical care, are less apt to follow through with care, and less likely to be involved in decisions related to their care (Muir-Cochrane, 2006). There is substantial evidence that those with SMI have significant difficulties following through with their routine health care and following healthy behaviors. For example, two studies noted that mortality rates are higher in this population than those without mental illness (Brown, Birtwistle, Roe, & Thompson, 1999; Saha, Chant, & McGrath, 2007). Patients suffering from SMI have higher obesity rates (Allison et al., 1999; Green, Patel, Goisman, Allison, & Blackburn, 2000), lower activity levels (Daumit et al., 2005), higher cardiovascular complications and high smoking rates (Goff et al., 2005).

An overall evaluation of patient activation in mental illness shows that activation levels are low in a mental health population when depression is noted to be high, and quality of life is low, according to the Short Form Quality of Life (SF-12) and Patient Health Questionnaire (PHQ-9), a depression scale (Magnezi, Glasser, Shalev, Sheiber, & Reuveni, 2014). The converse, high activation levels were associated with low levels of depression and high levels of quality of life, was also shown in this study (Magnezi et al., 2014). Moreover, a study by Sacks et al. (2014) indicates that activated patients have better long-term outcomes than less activated patients. One-year follow-up of patients who were more highly activated indicated that they also were managing their depression as evidenced by higher remission rates and lower PHQ-9 scores (Sacks et al., 2014). Chen et al. (2014) found that activation was greater when certain contextual factors, such

as familiarity of provider and high levels of community resources are available. This study gives evidence to the need for community resources and consistent care, which enhance patient activation levels (Chen et al., 2014).

Four studies were identified that evaluate interventions, such as increasing communication (Alegria et al., 2008), the use of the Health and Recovery Program (Druss et al., 2010), and the use of web-based technology to increase patient activation (Solomon, Wagner, & Goes, 2012; Solomon, 2010). Both communication and the use of a defined program had positive effects on increasing a patient's activation total scores, increased attendance at follow-up appointments, but did not improve empowerment (Alegria et al., 2008; Druss et al., 2010). Also, web-based technology was effective at changing activation levels, and recommendations were made to target specific levels of activation in these web-based interventions (Solomon et al., 2012; Solomon, 2010). When considering patient activation and its relationship to chronic illness and mental health diagnoses, having pharmacogenetic testing and medications prescribed based on these results, no published literature was found.

Medication Adherence Literature Review

A search for the term "medication adherence" and "medication compliance" on EBSCOhost with all databases chosen, yielded 13,726 and 14,320 respective articles. Limiting the search to peer-reviewed scholarly articles and full articles available, the result was 5,791 and 5,005". Also, limiting the date from 2000 to 2015 only excluded 50 articles. When the terms "mental health" and "chronic illness" were added, the articles were limited to 15. Through bibliographic references, additional articles were found resulting in a review of 22 articles. Ten articles were found when the terms

"pharmacogenetics or pharmacogenomics" were added to the search terms of "medication adherence" and "medication compliance." All of these articles were opinion articles, and only one study was identified in these ten articles as relevant to this dissertation topic.

Medication Adherence

Response to medication follows a known path; one must take the medication to have a positive effect from medication. Medication adherence or compliance is a multifaceted element within patient activation and includes a cascade of events that occur within the patient and between the patient and other entities, such as the physician and healthcare system (Dowell & Hudson, 1997). As described by Dowell & Hudson (1997), medication adherence as a concept, includes the patient's understanding and acceptance of their medical condition, their ability to try the medication, and their acceptance or non-acceptance of taking the medicine.

Research indicates that those who accept their illness and accept their medications are accountable (Dowell & Hudson, 1997). Additionally, studies report that those who felt like they had more input in their medications, thus more engagement in, had higher medication adherence rates (De Las Cuevas, Penate, & de Rivera, 2014). One qualitative study evaluating low-income, chronically ill participants, describe that medication compliance fell when patients did not have the feeling of sharing the decision with their provider (Mishra, Gioia, Childress, Barnet, & Webster, 2011). When a person feels there is little choice to take medication, psychological reactance occurs. This psychological reactance can be an important factor in medication adherence of antidepressants (De Las Cuevas, Penate, & Sanz, 2014). When self-efficacy was

evaluated, there was no effect on medication adherence (De Las Cuevas, Penate, & de Rivera, 2014). Interestingly, education given to patients regarding the medication and its use was also ineffective at increasing medication adherence (Gray, Wykes, & Gournay, 2002).

Medication non-adherence is significant in mental health because it affects patient outcomes, health care costs and increases depression relapses (Cantrell, Eaddy, Shah, Regan, & Sokol, 2006; Geddes et al., 2003; Melfi et al., 1998). Overall, those who are less educated, poor, and living in a rural area are less likely to be compliant especially with antipsychotic medications (Martin-Vazquez et al., 2011). Furthermore, those who are younger, have less understanding of their illness, and were diagnosed at an early age with schizophrenia were less compliant (Sarath Chandra, Lokesh Kumar, Pramod Reddy, & Pavan Kumar Reddy, 2014). In a study evaluating relapse in depression, three-fourths of those who took their medications as directed did not relapse (Geddes et al., 2003). Nevertheless, only half of patients who are taking antidepressants and are diagnosed with major depressive disorder are compliant with their medication regime after three months of use (Julius, Novitsky, & Dubin, 2009; Roca et al., 2011). Similarly, patients with schizophrenia have a 50-60% compliance, and bipolar patients have the lowest reported medication adherence at only 35 % (Colom et al., 2000; Lacro, Dunn, Dolder, Leckband, & Jeste, 2002; Perkins, 2002).

In complex patients with multimorbid disease diagnoses and mental health issues, medication adherence becomes more complex with each additional provider (Hansen et al., 2014). Hansen et al. (2014) found that the threshold of difficulty arises as soon as more than three providers are caring for a patient and prescribing medication.

Commonly, patients who are this complex have more than one provider (Parchman, Pugh, Noël, & Larme, 2002).

Provider expectations also have an impact on patient adherence and health outcomes as described by Byrne and Deane (2011); Byrne, Deane, and Caputi (2008). For instance, one study evaluated provider belief in the patient's ability to be compliant indicating a relationship of low expectations by providers yielding low adherence in patients (Byrne et al., 2008). Byrne and Deane (2011) later evaluated if the relationship between patient and provider affects medication adherence and found that a program aimed at understanding medications could not only foster increases in medication adherence but also enhance the patient-provider relationship.

The health care system, reimbursement, and other outside factors may also influence a patient's ability to remain compliant with medications (Dowell & Hudson, 1997). A qualitative study conducted by Kauppi, Hätönen, Adams, and Välimäki (2015) in which focus groups were conducted with providers and patients, reported that adherence was affected by the mental health system itself, relationships of providers, how follow-up was carried out, and the ability to take into account a patient's life view when prescribing medications. Patients in the qualitative study stated that they would like to know their provider and that this would help medication adherence. Additionally, patients have a learning curve associated with new medications and the language of healthcare (Kauppi et al., 2015).

Adverse effects may drastically affect medication adherence and are frequently to blame for patient's discontinuation of antipsychotic medication (Demyttenaere et al., 2001). In depressed patients, discontinuation of treatment occurs because of side effects

about 23-33% of the time (Hu et al., 2004). For example, the most common adverse effects reported for the antidepressant Nortriptyline are dry mouth, blurred vision, dizziness upon standing, and urinary symptoms, which are very similar to other antidepressant medications. These contributed to medication discontinuation in the genome-based therapeutic drugs for depression (GENDEP) study (Uher et al., 2009). This study also noted that side effects occurred at the beginning of treatment and decreased over time (Uher et al., 2009).

A German study evaluated patient medication adherence and serum blood levels, finding inconsistencies that may be attributed to pharmacogenetic effects (Stieffenhofer & Hiemke, 2010). For example, those who had genetically higher enzymatic activity, which is called ultra-rapid metabolism (UR), through the CYP genetics, had lower serum concentration of medication. Additionally, those who were genetically poor enzymatic metabolizers (PM) had higher serum medication levels. Therefore, while patient medication adherence may affect drug levels, pharmacogenetics may also play a role.

One sentinel study by Fagerness et al. (2014) evaluated insurance claims data for patients who had received pharmacogenetic testing and medication guidance based on the results of testing. When compared to a control group of patients without genetic testing, the patients who received pharmacogenetic testing filed fewer insurance claims resulting in a $546 savings per patient over a four months' interval. Additionally, the patients who had pharmacogenetic testing had claims data indicating increased medication compliance when compared to the control group (Fagerness et al., 2014). It has been recognized that the potential for this increased medication compliance could be related to the opening of communications between the provider and patient regarding medications and their

suitability based on genetic testing (Haga & LaPointe, 2013). However, no identified studies have focused on communication, pharmacogenetics and medication adherence.

Pharmacogenetics in clinical practice

'Pharmacogenetics,' a term coined by Friedrich Vogel in 1959, is the study of drugs as they relate to a person's genetic make-up (Eichelbaum, Ingelman-Sundberg, & Evans, 2006; Vogel, 1959). Specifically, pharmacogenetics refers to the interaction of drugs and the genetic makeup affecting the protein production in the cytochrome (CYP 450) enzymatic pathways of the liver (Ma, Lee, & Kuo, 2012). Consequently, this affects drug metabolism by modification of enzyme activity within the pathway (Ma et al., 2012). Pharmacogenetic testing is an innovative approach to finding the "right drug" for the "right person" (Eichelbaum et al., 2006).

As previously noted, open communications are required between provider and patient when genetic testing occurs. This communication is set in South Dakota state law as of 2001 and includes appropriate informed consent from the patient regardless of study participation. Standard of care when laboratory tests are ordered is that a provider discusses the results with the patient and how the treatment plan may change based on the ordered test. This study requires documentation of acknowledgment that medications will be changed or confirmed based on the pharmacogenetic testing (South Dakota State Legislature, 2001).

The Pharmacogenetics Research Network (PGRN) was developed in the year 2000 through the National Institutes of Health (NIH) and is composed of a multi-disciplinary group established to evaluate pharmacogenomic impact on health (Pharmacogenetic Research Network, 2015). It is through the PGRN that the Clinical

Pharmacogenetic Implementation Consortium (CPIC) has put together evidence-based guidelines for the use of pharmacogenetics in practice. The Dutch Pharmacogenetic Working group (DPGW) is another consortium within the Netherlands who also have evidence-based guidelines available for clinical practice. Between the two consortiums, there are 78 evidence-based guidelines available to prescribing providers for guidance on various medications in clinical practice (Whirl-Carrillo et al., 2012).

The use of the PharmGKB website at Stanford houses the CPIC and DPWG clinical guidelines and continues to add to the science by conducting an analysis of applicable publications which may be utilized in clinical practice (PharmGKB, 2015). The availability of these resources has aided the acceptability and clinical use of pharmacogenetics. For example, the Food and Drug Administration (FDA) has approximately 120 medications which have metabolic relationships to specific genetic pathways and are listed in patient medication pamphlets (FDA, 2014; Haga, Mills, & Bosworth, 2014). Please refer to Appendix B for clinical guideline resources and education in pharmacogenetics.

Other contributions to the clinical use of pharmacogenetics include decreasing costs and increasing research interest and knowledge. Costs for processing pharmacogenetic samples have decreased as technology has advanced, causing an increase in research interest and clinical practice (Wu & Fuhlbrigge, 2008). These research interests have focused on specific allele groups and their effect on medications. Alleles are one of two forms of a gene that have occurred because of mutations, substitutions or deletions of nucleotides or proteins and result in different physical traits or phenotypes. Having blue eyes or having a CYP 450 pathway with poor metabolic

enzyme activity, both represent phenotypes (Zhou et al., 2009). An allelic composition, as it relates to pharmacogenetics, establishes the enzymatic abilities within the liver. Most medications are metabolized, or activated through the CYP 450 enzymatic system, and this accounts for how approximately 75% of medications are either activated or cleared from the body. The remaining 25% are metabolized through alternative body systems, e.g. kidney. (Furge & Guengerich, 2006; Guengerich, 2008).

Overall, pharmacogenetic testing includes evaluation of the genes responsible for enzyme production throughout the CYP 450 liver metabolic pathways (Ingelman-Sundberg, 2001, 2004; Ingelman-Sundberg & Rodriguez-Antona, 2005). Each genetic result provides a picture of how well or how poorly the enzyme functions in an individual pathway to either activate the medication or degrade the medication for elimination. Depending on the combination of alleles in the genes inherited by the parents, a person may have normal metabolism, otherwise described as extensive metabolism (EM), intermediate metabolism (IM), poor metabolism (PM), or ultra-rapid metabolism (UR) (Ingelman-Sundberg, 2001, 2004; Ingelman-Sundberg & Rodriguez-Antona, 2005). These results affect the ability of the liver to either convert a medication to its active form or break down the medication for excretion. When the enzyme activity is increased, as in ultra-rapid metabolism (UR), the medication will be quickly metabolized and the patient may not see the benefit of the drug or will not have benefit of the drug's positive effects for the length of normal time metabolizers (EM) do (Mrazek, 2010b).

A clinical example of pharmacogenetics in practice was the point of an FDA warning regarding children and the use of post-surgical codeine in children who are ultra-rapid metabolizers at CYP 2D6 (Food and Drug Administration, 2013). When children

who are ultra-rapid metabolizers at CYP 2D6 have normal doses of codeine, the increased enzymatic activity converts codeine to morphine very quickly, which in turn increases morphine blood levels causing respiratory decreases or arrest (Food and Drug Administration, 2013), Poor metabolizers, on the other hand, are unable to break down the medication to convert it to morphine and therefore, may not perceive the benefit of the medication, plus may exhibit increases in side effects (Mrazek, 2010b; Mrazek et al., 2014).

Pharmacogenetics in Mental Health

The primary CYP enzyme pathways involved in antipsychotic medication metabolism in the liver include; CYP 1A2, CYP 2D6, CYP 3A4, and CYP 2C19. Within each CYP pathway, variability of allelic composition exists. An allelic variant is an alternate form of a gene; one allele is inherited from each parent. These allelic variations influence the metabolism of a drug (Guengerich, 2008). Additionally, transporter and receptor genes are important in psychotropic medication metabolism and transport and include; OPRM1, SLC6A4, HTR2A, and COMT.

Indiana University website, http://medicine.iupui.edu/clinpharm/ddis/main-table, lists medications according to their major pathway of excretion or activation. Medications are classified as substrates, inhibitors, and inducers. A substrate is a medication that passes through a specified CYP pathway, and the enzymatic activity breaks down the medication. An Inhibitor is a medication that blocks or inhibits the enzymatic activity from breaking down another medication that utilizes the same pathway. An inducer is a medication that increases the activity of the enzyme causing an increased rate of breakdown of a medication (Flockhart, 2007).

The pharmacists working on the study have developed a table of psychotropic medication utilized in this study and their associated CYP pathways (Appendix C). Medications can be substrates, inhibitors or inducers of a CYP pathway. For example, a substrate is a medication that utilizes the pathway, an inhibitor blocks the pathway for other medications, and an inducer increases the enzymatic breakdown of the medication (Zhou et al., 2009). A table related to medications for this study indicates psychotropic medications that will be utilized in this study and denotes the CYP pathway utilized along with if the medication is a substrate, inhibitor or inducer of a CYP pathway (Appendix C). Magro, Moretti, and Leone (2012) described types of interactions such as Drug-Drug Interactions (DDI), Drug-Gene interactions (DGI) and Drug-Drug-Gene Interactions (DDGI). Commonly, Drug-Drug interactions are to blame for adverse drug reactions in persons taking two or more medications (Magro et al., 2012). A recent study by Verbeurgt, Mamiya, and Oesterheld (2014) noted that in addition to DDI there are DGI, and DDGI that take place. These interactions are much more frequent than most realized. DDI's are caused when two drugs alter another drug's effect on the body or interfere with metabolism, distribution or excretion of another drug. DGI's are an interaction between the drug and genetic makeup of the person, such as interference in the liver's CYP 450 enzymatic pathways (Verbeurgt et al., 2014). DDGI's occur when there are drug-drug interactions and drug-gene interactions affecting several CYP 450 pathways (Verbeurgt et al., 2014). This study notes that DDI's account for 66.1% of interactions, but that the remaining 33% were associated to DGI, and DDGI's (Verbeurgt et al., 2014). Accounting for this information, it suggests that pharmacogenetic testing may increase a provider's ability to prescribe a drug that will not cause adverse effects.

The pharmacogenetic report will include the genetic results and medication changes recommended by a pharmacist team. The provider and patient communication will include an acknowledgment by the patient that their medications are based on their genetic profile. The reports will include suggestions individualize to the patient's current medication list and genetic profile. For example, if a patient has a resulting genetic panel that results in poor metabolism of the CYP 2D6 pathway and is taking fluvoxamine, which is metabolized primarily by this pathway, an alternate medication recommendation would be provided. Additionally, the report will list medications that should be avoided with this patient.

Gaps between genetics and behavioral outcomes

Very little research has focused on the influence of having genetic testing on patient behavior, specifically pharmacogenetic testing. Haga and LaPointe (2013) have speculated that the act of pharmacogenetic testing will increase a patient's medication adherence. Additionally, Haga and LaPointe (2013) point out other positive impacts of pharmacogenetic testing such as less need for medication dosing adjustments, fewer changes in medications, fewer side effects, and the potential of less time to therapeutic outcomes. These factors may contribute to medication adherence after pharmacogenetic testing. However, there is only one identified publication that has addressed these two topics together using pharmacy refill data (Fagerness et al., 2014).

Three studies addressed medication adherence in patients who have had genetic testing, two studies evaluated risk genes and medication adherence, while one evaluated pharmacogenetic testing and insurance information on medication refill data (Charland et al., 2014; Fagerness et al., 2014; Grant et al., 2009). Grant et al. (2009) conducted a

survey of participants in type 2 diabetes trials with and without a diabetes and reported that they would be more likely to have higher motivation to change their lifestyle if they had a 'high risk' gene for diabetes. Additionally, participants reported that they would be 'much more motivated' to be compliant with their medications if they had the high-risk gene (Grant et al., 2009). Additionally, Charland et al. (2014) evaluated adherence to statin medications after risk testing of the KIF6 gene which shows an increased risk for congestive heart disease, finding that adherence increased with the knowledge of the result of this genetic testing. The difference here is that the KIF6 gene is a risk gene and does not affect medication metabolism. However, the finding implies that having the genetic result of increased risk, increases a person's motivation to become more compliant. One recent study evaluated retrospective health claims and concluded that those participants who had pharmacogenetic testing were more adherent to their medication as noted by medication refill data (Fagerness et al., 2014).

Medication adherence and patient activation have been noted to be low in patients with mental health disorders (Gunn et al., 2012; R. Sacks et al., 2014; Whooley et al., 2008). As defined by Hibbard (2008) activation refers to how engaged one is in managing his or her healthcare and can change over time. It follows that if pharmacogenetics may improve a patient's medication adherence, which is a component of patient activation, overall activation may also improve. The amount of activation a patient may have in his or her healthcare is variable based on patient interest, skills, and the capacity to understand the diagnoses (Von Korff et al., 1997).

Patient activation improves not only medication adherence but also health outcomes. When a patient is activated or engaged in their healthcare, increases in health-

related behaviors are noticed including improved diet, exercise and obtaining preventative screening tests (Hibbard et al., 2004). Four studies indicated that high patient activation measures correlate to better health outcomes in biometric indicators of health such as blood pressures, HgA1C levels, cholesterol levels, and body mass index (Hibbard & Greene, 2013; Rogvi et al., 2012; R. Sacks et al., 2014; Skolasky et al., 2011). To date, there are no published prospective studies identified which have studied patient response to pharmacogenetic testing as a relationship to medication adherence and patient activation.

This research study seeks to address the gaps in the literature found regarding patient activation, medication adherence and pharmacogenetic testing in a mental health and chronic illness patient population. The purpose of the study is to compare the outcomes of patient activation and medication adherence before and after medication recommendations have been made utilizing pharmacogenetic testing information in a chronic illness and mental health population. Research is needed to explore pharmacogenetics and potential behavioral changes. No published studies were found by this author addressing pharmacogenetics and patient activation. Additionally, only one published study was found by this author which examined medication adherence as the relationship of medication refill data to pharmacogenetics. No published studies were identified by this author evaluating pharmacogenetics in patients with complex medical and medication backgrounds including mental health diagnoses and chronic illnesses.

Theoretical Framework

Davies et al. (2010) introduced a theoretical framework targeted to the practicing clinician. It was developed by evaluating challenges that clinicians face when choosing antipsychotic medications. The challenges are that a provider must be aware of and knowledgeable regarding pharmacology of drugs, molecular genetics of drug targets, and genetics of drug metabolism to prescribe medications according to genetics. The conceptual framework emphasizes the patient outcomes related to medication adherence, side effects of medications and effectiveness of the medications (Davies et al., 2010).

Within this conceptual framework, medication monitoring, medication planning, molecular genetics of drug absorption and metabolism and patient outcomes are described. These elements will be incorporated into Orem's theory of self-care to provide the framework and the theoretical basis for the study. This study will be addressing the molecular genetics of drug targets and metabolism as they relate to patient adherence, activation and thus patient outcomes.

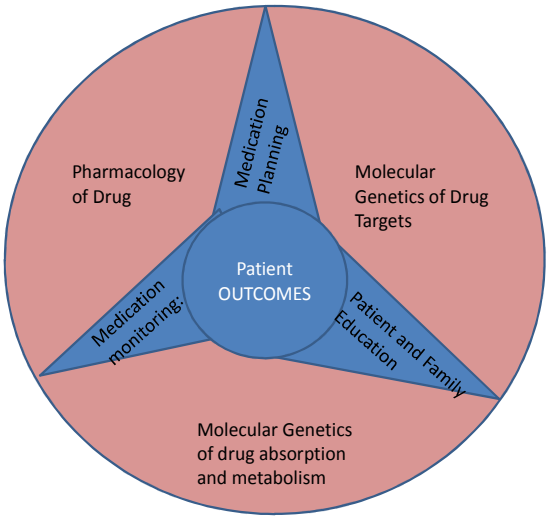

Figure 1. Conceptual framework incorporating pharmacologic findings and pharmacogenetic evidence about atypical antipsychotic medications (AADs) into advanced psychiatric nursing practice Davies, M. A., Conley, Y., & Puskar, K. (2010). Incorporating evidence from pharmacologic and pharmacogenetic studies of atypical antipsychotic drugs into advanced psychiatric nursing practice. *Perspectives of Psychiatric Care, 46*(2), p.99

Nursing Perspective

Dorothea Orem's Self-Care Deficit Theory (SCDT) theoretical emergence came from influences of philosophers such as Aristotle, Thomas Aquinas, Harre and Wallace and influenced the assumptions underlying her theory (Orem, 2006). In Orem and Taylor (2011, p. 36)'s last reflections on her philosophic determinants, it was expressed that she followed a "*moderate realism"*, which was clarified as a practical scientific method, with applications of nursing science to practical reality. In an effort to define nursing science, the grand theory of SCDT emerged (Orem & Taylor, 1986, 2011)**.**

Three mid-range theories, which are interrelated, comprise the grand theory of SCDT. These intertwined theories include concepts, assumptions about the theory, and

interrelationships between the theories. The three theories are; the Theory of Self-Care, Theory of Self-Care Deficit, and the Theory of Nursing Systems (Parker & Smith, 2010). Figure 2 illustrates how the Theory of Self-Care is a subset of the Theory of Self-Care Deficit, which is a subset of the overarching Theory of Nursing System.

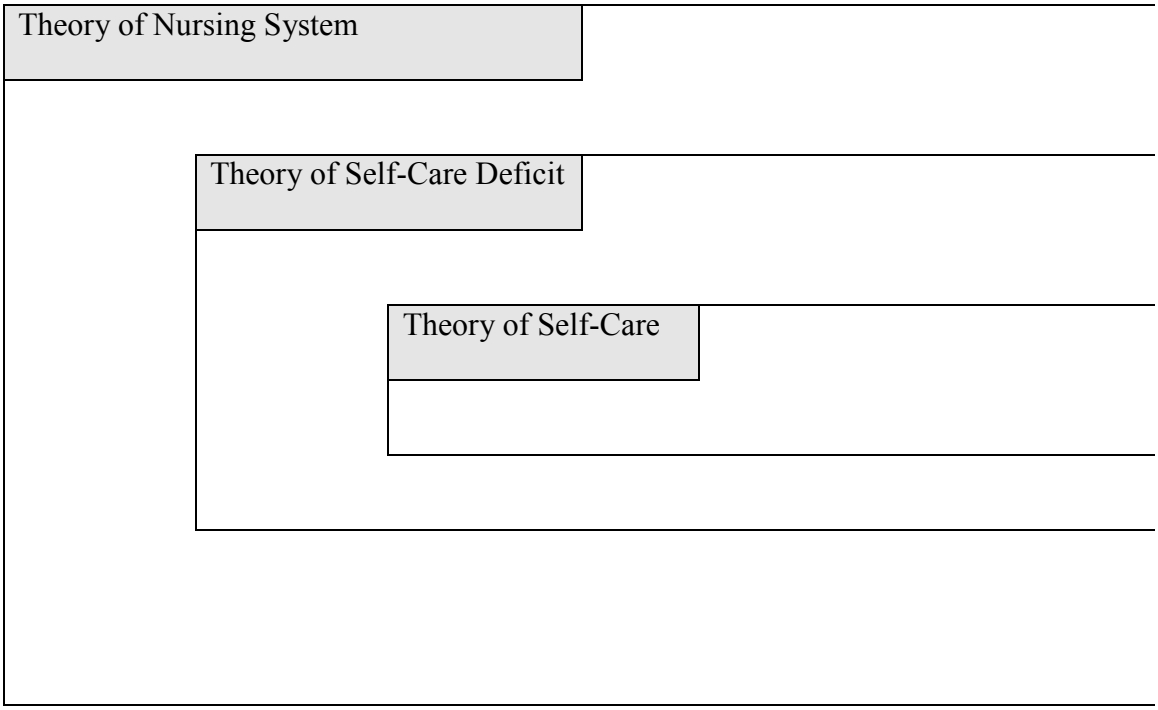

Figure 2. Constituent theories, the self-care deficit theory of nursing.
Orem, D. (1995). Nursing Concepts of Practice (5th Ed.) St. Louis: Mosby. (p.172)

Theory of Self-Care

The ideas behind self-care began with the simple question, "Why do people need nursing?" (Renpenning & Taylor, 2003, p. 261 of 6936). The term was coined in 1956 when Orem was describing nursing in an Indiana State Health report (Orem, 1971; Orem, 2006). The theory of self-care has three central concepts which include; self-care, self-care agency and self-care requisites, as depicted in Figure 3 below (Denyes et al., 2001;

Nursing Development Conference Group, 1979). Renpenning and Taylor (2003, p. 3816 of 6936) wrote from "personal knowledge", one of the emergent definitions of self-care as;

> *"Self-care is conceptualized as the personal care that human beings require each day and that may be modified by health care, environmental conditions, effects of medical care and other factors."*

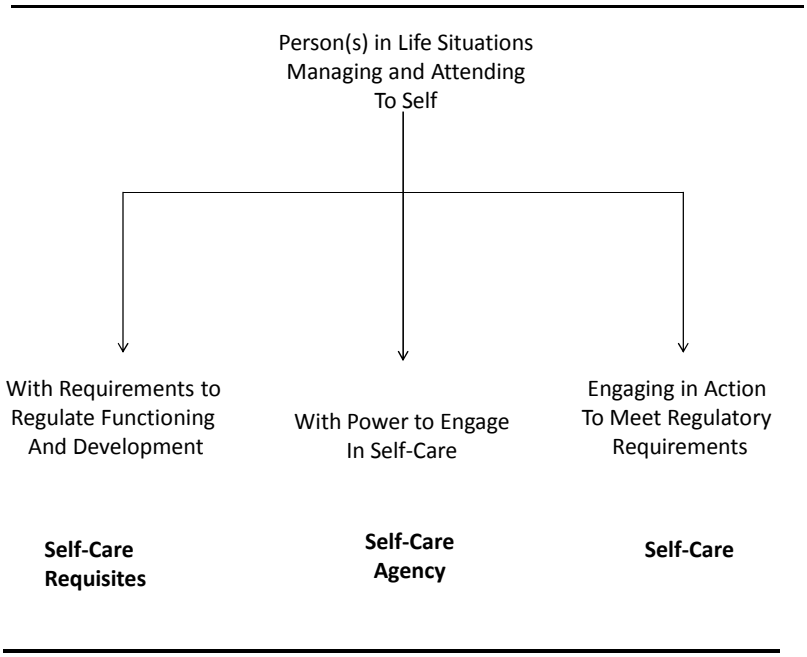

Figure 3. Denyes, M., Orem, D., & Bekel, G. (2001). Self-care: A foundational science. *Nursing Science Quarterly, 14*(1), p.49.

Self-Care. The concept of self-care identifies the "self" as both the entity performing the action or the "action agent" and the recipient of care. Self-care is purposeful behavior, which contributes to the overall wellness of an individual. The presuppositions of self-care are that it is a learned, voluntary behavior and responsibility or a right of the individual to maintain health and wellness (Denyes et al., 2001; Nursing Development Conference Group, 1979).

The propositions include understanding self-care from three perspectives that contribute to overall self-care and include; (a) conditioning factors, (b) psychophysiological factors contributing to health and disease states, and (c) behavioral resources and demands (Denyes et al., 2001). Conditioning factors include; having abilities related to understanding self, having a self-concept, understanding family and social positions, along with maturity levels. Psycho physiological factors which contribute to health include self-care maintenance or the ability to maintain balance within the self, ability to perform tasks to maintain health, and ability to obtain or have knowledge of what needs to be completed to maintain health. For example, anything that disrupts the balance may cause illness and affect one's abilities of self-care. Moreover, self-care behavioral resources that include one's motivation, and use of resources (Nursing Development Conference Group, 1979).

Self-care requisites. Self-care requisites are generalized actions required to maintain a purpose. Additionally, within self-care, there are three main categories of self-care requisites including; universal, developmental and health-derived (Orem, 2001; Renpenning & Taylor, 2003).

Universal self-care requisites include commonalities to all humans at all ages, such as the need to sleep, eat, and exercise. Nurses have the ability to identify a patient's maturation process and adapt nursing interventions towards those developmental requisites. Developmental health care requisites occur across the lifespan and are the changes one has as one ages including cognitive and affective changes. Health-derived requisites are biologically based changes to structure and function of the body and represent a need for nursing care (Orem, 2001; Renpenning & Taylor, 2003; Taylor,

Renpenning, Geden, Neuman, & Hart, 2001). Orem (2001) identified six types of health-derived requisites including; the ability to seek and gain medical assistance, identifying changes in one's health status, following through with prescribed treatments, awareness of and attendance to negative effects of treatment, adjusting self-image as health status changes, and living with health conditions as they arise (Orem, 2001).

Renpenning and Taylor (2003) published collections of Dorothea Orem's unpublished writings notes which had been presented at meetings. This collection also refers to "therapeutic self-care demand" as a requisite. Orem defines this as

> " *care measures or self-care or dependent-care practices which result from investigation of questions about how self-care requisites can be met under prevailing conditions"* (Renpenning & Taylor, 2003, p. 3930 of 6936).

Therefore, when self-care demand is overwhelming to the person's self-care capabilities, nursing assistance is needed (Orem, 2006).

Self-care agency. Self-care agency is the power and ability to care for the self, and therefore nursing agency is the capability, knowledge and insight into the patients needs as self-care agents with deficits (Renpenning & Taylor, 2003). Motivation and motives are the basis for self-care agency along with action. Motivation, however, is a complex concept with two actionable concepts; (a) there must be a deliberate goal seeking action; (b) There must be a relationship between the motivation and deliberate action (Renpenning & Taylor, 2003). In addition, there are six conditions that may promote self-care agency; (a) people must be knowledgeable to see what is good and bad in their pursuit of a goal; (b) people must have a reason that is personalized as desirable; (c) people need time to formulate and visualize a plan of action; (d) people should reflect

on their actions to determine suitability of the actions; (e) people should end their reflection time; (f) people must be responsible for their choice of action to attain the goal (Orem, 1987; Renpenning & Taylor, 2003).

Study framework. Orem's Theory of Self-care, patient activation, medication adherence and pharmacogenetic framework are used as the study's complete framework to help describe the behavioral components of self-care after pharmacogenetic testing, and medication changes have been implemented. This study will measure Patient activation (PAM-MH) and as evidence of the components of Self-Care, Self-Care Agency, and Self-Care Requisites. For the pharmacogenetic testing framework for this study see Figure 4.

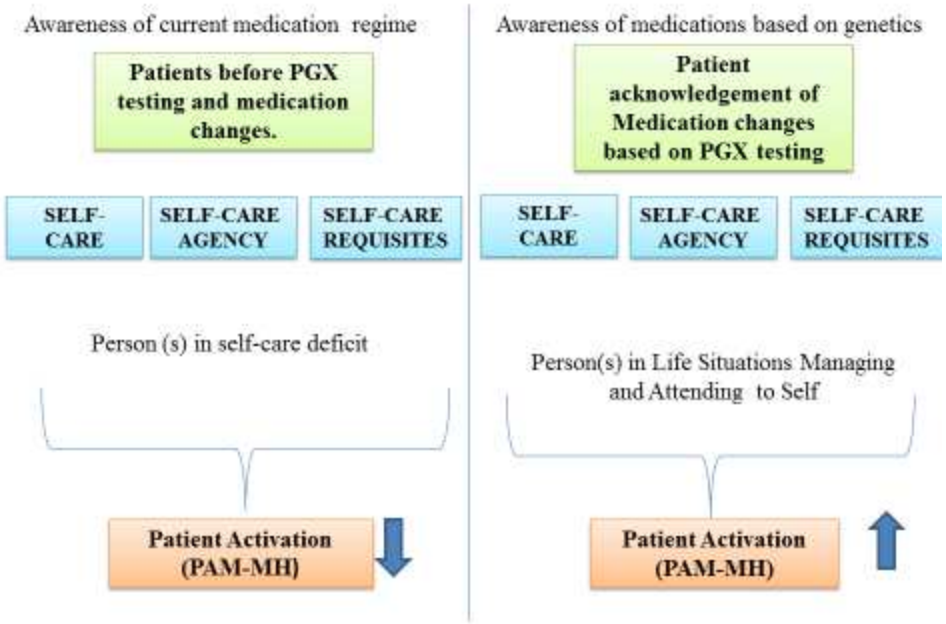

Figure 4. Patient activation as evidence of Self-Care.

Summary

This literature review and discussion of theoretical basis have identified the concepts that are significant to the design and implementation of this study. The purpose of the study is to compare the outcome of patient activation before and after medication recommendations have been made utilizing pharmacogenetic testing information in a chronic illness and mental health population.

Studies have been conducted in patients with significant mental illness with regards to patient activation. However, no studies identified by this author have addressed patient activation in patients who have had pharmacogenetic testing. Pharmacogenetics is gaining clinical acceptance as evidence for its applications within the mental health population grows. No research exists related to behavioral outcomes of pharmacogenetic testing in this population. Therefore, this study is designed to address the gaps in the literature as they relate to aspects of patient activation in patients with serious mental illness after pharmacogenetic testing and implementation. This study will add to knowledge and understanding of behavioral aspects of pharmacogenetic testing and medication planning based on testing, patient activation and medication adherence.

CHAPTER 3

DEPRESSION OUTCOMES IN CARE COORDINATION, PRIMARY CARE AND PSYCHIATRY PATIENTS AFTER PHARMACOGENETIC TESTING.

Introduction to study changes

The study of patient activation in mental health patients after having pharmacogenetics care in a care coordination population was discontinued in January 2016 due to an administration reason. When the study concluded, there were 26 participants with 100 required, and enrollment was progressing slowly. This chapter discusses the combination of data from three studies. The purpose of this dissertation study was to evaluate by provider types of care coordination, primary care and psychiatry, the change of depression severity (PHQ-9), depressive symptoms (QIDS-SR16) and quality of life (SF-36) over time (T1-T3) in a population of patients diagnosed with MDD or DDNOS after having had pharmacogenetic testing.

The data from the care coordination study was combined with data collected from two additional studies that evaluated pharmacogenetics testing in people diagnosed with depression. All studies included a pharmacist guided medication recommendation for each participating patient, and these recommendations were given to providers in a report called the pharmacogenetics report (PGXr). The term "pharmacogenetics care" will be used to represent the process of medication recommendation reporting based on genetics and genetic testing which occurred in all of these studies. This process includes the fact that by entering the study and having genetic testing, study participants' medications for depression were managed based on their genetics. All studies were conducted with

patients who were diagnosed with new or current major depressive disorder (MDD) or depression disorder- not otherwise specified (DDNOS). The similarities and differences of these studies will be explained.

The main differences between the three studies was the type of provider managing the patient's depression. One study evaluated a population of patients who had specialists, psychiatrists, managing their depressive disorder. This study will be referred to as 'psychiatry' throughout this document. While the other two studies focused on patients, who were managed by primary care providers. The care coordination study focused on patients with complex medical concerns under the management of a primary care provider and the patient was participating in care coordination. The care coordination study utilized a nurse or social worker to help navigate through the health system and manage care. The third study had depression management through primary care, and will be referred to as the 'primary care' study. While patient activation was a component of the care coordination study, it was not included in the other two studies. Therefore, no patient activation data will be analyzed.

All participants completed the same questionnaires including, a) an assessment of depression severity, Patient Health Questionnaire 9 (PHQ-9), b) an assessment of depression symptoms, The Quick Inventory for Depressive Symptoms- Self Report (QIDS-SR16) and c) an assessment of quality of life, The Short Form 36 (SF36). Additionally, questionnaire collection was completed on the same timeline and visit schedules in all three studies. Completion of questionnaires occurred at baseline (T1), at the time the pharmacogenetics medication recommendations report (PGXr) was returned to their provider, (T2), and one month after medication changes were made (T3).

Demographic information such as age, marital status, insurance type, number of mental health diagnoses, and number of chronic health conditions were also collected.

These three depression studies were designed to evaluate the use and impact of a comprehensive pharmacogenetic report prepared by genetic pharmacists in the three settings. All three groups received pharmacogenetic testing, and providers were given a pharmacists guided report with medication recommendations based on the patient's genetics. Patients acknowledged that they would have medications modified based on this genetics report during the consenting process, and subsequent provider discussions regarding the report.

The genetic reports took into account each patient's genetic variants as they relate to their enzyme activity of drug metabolism. The reports also included information related to interactions between genes and other medications, such as, drug-drug, drug-gene and drug-drug-gene interactions (Magro et al., 2012; Verbeurgt et al., 2014). The testing focused on genetic pathways associated with antidepressant and antipsychotic medications, see appendix A. This report included a list of medications classified into three categories, "use as recommended", "use with caution", or "not recommended", for each patient's medication list. This report was given to the providers at four weeks or at 12 weeks in two of the studies. The care coordination study patients had reports prepared for providers at four weeks without randomization.

In summary, these three studies shared a similar population of patients all of which had a diagnosis of depression (MDD or DDNOS), data from the PHQ9, QIDS-SR, and the SF-36, which were completed at the same intervals, and all studies had pharmacogenetic testing with comprehensive pharmacogenetic care (PGXr). These

likenesses allowed for data combination and analysis. The three studies are described in detail. (Table 1) describing similarities and differences of the three studies.

Table 1

Comparison of three provider types

Study	Primary Care	Specialists Care (Psychiatry)	Care Coordination Study
population	outpatient primary care	outpatient psychiatric care	outpatient primary care (care coordination participants)
diagnoses	depression (MDD or DDNOS)	depression (MDD or DDNOS)	*depression, bipolar, schizophrenia
depression questionnaire	PHQ9	PHQ9	PHQ9
symptoms questionnaire	QIDS-SR16	QIDS-SR16	QIDS-SR16
Quality of life questionnaire	SF-36	SF-36	SF-36
Randomization	PGXr received by provider at 4 weeks or 12 weeks	PGXr received by provider at 4 weeks or 12 weeks	No randomization occurred.

Care Coordination study

The initial dissertation study is referred to as the care coordination study and was evaluating mental health patients' activation in a care coordination population after receiving pharmacogenetic care. This study enrolled patients with MDD or DDNOS. In addition to these depression diagnoses, these care coordination participants had significant chronic illnesses and other mental health diagnoses in addition to depression.

Patients typically enter care coordination through recommendations made by their primary care providers having met the criteria for the program. Care coordination

patients were accepted into the care coordination program based on the number of hospitalizations, number of medications and chronic diagnoses. Tier selection based on hospitalizaitons and providers caring for the patient are presented (Table 2). If a patient has more than two medications with a visit to the emergency department, and, at least, two providers, the patient could be admitted to the lowest level of care coordination. The highest level of care coordination includes patients who were taking more than nine medications, has had two or more emergency room visits, two or more inpatient hospitalizations, and was seeing eight or more providers. The care coordination patients had a nurse and a social worker assigned to them to help navigate the health care system.

Table 2.

Care Coordination Tiers

Tier 1	**Tier 2**	**Tier 3**	**Tier 4**
1 - 2 medications	3 – 4 medications	6- 8 medications	9 + medications
1* ER visit	1 ER visit	2 ER visit	2+ *ER visits
0 IP Admits	1 IP Admit	2 IP Admits, including 1 readmit	2+ IP Admits including 2 readmits
1- 2 physicians providing services	3- 4 physicians providing services	5 –7 physicians providing services	8+ physicians providing services
*Hx: one diagnosis and/or complaint	Hx: 2-3 diagnoses and/or complaints	Hx: 4 – 5 diagnoses and/or complaints	Hx: 6 + diagnoses and/or complaints

***Hx = History; ER = Emergency Room**

Primary Care study

Primary care providers who manage patients with depression were eligible to refer patients to this study. All participants continued to work with their primary care providers for management of their depression. Patients who qualified for this study must

have scored ten or greater on the Patient Health Questionnaire (PHQ-9) indicating current depressive symptoms and the need for treatment alteration or dose escalation. A high score on the PHQ9, indicates more severe depression. Participants had a baseline assessment of their depression severity (PHQ9), depressive symptoms (QIDS-SR16) and quality of life (SF-36). This study was a six-month study, with blinded randomization. Patients were randomized to either having their provider receive their report at four weeks or 12 weeks, (Table 3).

Psychiatry

The Specialists study 'psychiatry' included the same population of patients. However, these patients were being provided care by psychiatry instead of primary care. All other assessments and randomizations were the same. Data collection and timing were similar in all studies (Table 1) (Table 3).

Randomization in two of the three studies

Participants in the primary care and psychiatry studies were randomized to receive the PGXr at four weeks or twelve weeks. Participants who were randomized to the four-week arm of the study, were assessed by their first and third visits; baseline (T1), and one month after recommendations had been made (T3). The participants who received randomization at 12 weeks were assessed at baseline (T1), at the time they received PGXr at 12 weeks (T2) and one month after receiving their reports (T3). All patients completed the same assessments including the PHQ-9, QIDS-SR, and the SF36 at each visit. Evaluations and timelines are presented in (Table 1) and (Table 3) for the evaluations and timeline. All three studies were approved by the health systems local Institutional Review Board. See appendices D for the Institutional Review Board

approval, E for the Informed consent and supporting documents, F for the patient invitation letter, G for IRB approval Amendment 2.

Table 3

Data collection time-points

ALL STUDIES COLLECTED			
Assessment	**Baseline T1**	**PGX results T2**	**1 month after results returned T3**
PHQ-9	x	x	x
QOL	x	x	x
QIDS-SR	x	x	x

T1 = Time 1, T2 = Time 2, T3 = Time 3

Problem statement

Depression is a significant problem in the United States, and many who suffer from depression do not achieve remission of depressive symptoms and, or, develop side effects from medications (Ishak et al., 2013; World Health Organization, 2015). In a literature search, there were three sentinel studies identified, indicating comparisons of primary care and psychiatry providers, but no studies were identified that evaluated depression outcomes of patients participating in care coordination with comparisons to primary care or psychiatry patients (Gaynes et al., 2005; Gaynes et al., 2007; Simon, Von Korff, Rutter, & Peterson, 2001).

A study by Simon et al. (2001) concluded that both primary care and psychiatry patients had improvement in their depression and quality of life scores, and reported that

there were not any differences of depression severity between the two groups (Simon et al., 2001). Gaynes et al. (2007) findings supported that primary care and psychiatry providers have similar outcomes and have patients with similar depression severity. On the other hand, conflicting information was found regarding suicidal ideation. The study by Gaynes et al. (2005) indicated that those patients who were managed by psychiatrists had a higher incidence of suicidial ideation and past suicide attempts compared to primary care patients, but then found later that suicidal ideation was equal in both provider groups. This study also reported that primary care patients were less likely to self-select as having a depressed mood and had the inability to experience pleasure, i.e., anhedonia, indicating a potential to under report symptoms (Gaynes et al., 2005).

The study by Simon et al. (2001) also found that there were deficiencies in both primary care and psychiatry providers, such as poor follow-up with patients after they leave the clinic. The study also recommended adding more care management options to improve patient compliance and potentially outcomes (Simon et al., 2001). In fact, a study completed earlier by the same group identified that when a patient has systematic follow-up from a care manager, depression did improve (Simon & Ludman, 2000). However, a comparison of care management such as care coordination to both primary care and psychiatry was not identified in a literature review. The literature review did not reveal any commparisons of baseline differences in depression, or changes over time between a care coordination population compared to those patients who are managed by primary care or psychiatry.

Table 4

Comparison of three studies

Study	Primary Care	Specialists Care (Psychiatry)	Care Coordination Study
population	outpatient primary care	outpatient psychiatric care	outpatient primary care (care coordination participants)
diagnoses	depression (MDD or DDNOS)	depression (MDD or DDNOS)	*depression, bipolar, schizophrenia
depression questionnaire	PHQ9	PHQ9	PHQ9
symptoms questionnaire	QIDS-SR16	QIDS-SR16	QIDS-SR16
Quality of life questionnaire	SF-36	SF-36	SF-36
Randomization	PGXr received by provider at 4 weeks or 12 weeks	PGXr received by provider at 4 weeks or 12 weeks	No randomization occurred.

*Care coordination allowed additional diagnoses as listed

Purpose of this study

The purpose of this study was to evaluate by provider types including care coordination, primary care and psychiatry, the change of depression severity (PHQ-9), depressive symptoms (QIDS-SR16) and quality of life (SF-36) over time (T1-T3) in a population of patients diagnosed with MDD or DDNOS after having had pharmacogenetic testing.

Research questions

1. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in depression severity (PHQ9) over time (T1-T3) based on the type of provider?

a. Hypothesis 1: Depression severity scores (PHQ9) among patients who receive care coordination will decrease over time.

b. Hypothesis 2: Depression severity scores (PHQ9) among patients who receive care by a Primary care provider will decrease over time.

c. Hypothesis 3: Depression severity scores (PHQ9) among patients who receive care by a Psychiatrist will decrease over time.

2. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in depression symptoms (QIDS-SR16) over time (T1-T3) based on provider type?

    a. Hypothesis 1: Depression symptom scores (QIDS-SR16) will decrease over time (T1-3) among patients who receive care coordination.

    b. Hypothesis 2: Depression symptoms scores (QIDS-SR16) will decrease over time (T1-T3) among patients who receive Primary care services.

    c. Hypothesis 3: Depression symptoms scores (QIDS-SR16) will decrease over time (T1-T3) among patients who receive care through psychiatry.

3. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in the physical components (physical functioning, role physical, bodily pain, general health) of the SF-36 scale by provider type?

    a. Hypothesis 1: Overall physical component scores (PCS) of the SF-36 scale will be highest in psychiatry and primary care, and lowest in care coordination.

b. Hypothesis 2: When comparing by provider types, physical functioning scores in the SF-36 scale will be the highest in psychiatry and primary care and the lowest in care coordination.

c. Hypothesis 3: When comparing by provider types Role Physical scores in the SF-36 scale will be highest in psychiatry, and primary care and lowest in care coordination.

d. Hypothesis 4: When comparing by provider types, Bodily Pain scores in the SF-36 scale will be highest in psychiatry and Primary care and lowest in care coordination.

e. Hypothesis 5: When comparing by provider types, General Health scores in the SF-36 scale will be highest in psychiatry and Primary care and lowest in care coordination.

4. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in the mental components (vitality, social function, role emotion, and mental health) of the SF-36 scale by provider type?

   a. Hypothesis 1: When comparing by provider types, mental composite scores of the SF-36 scale will be highest in primary care and care coordination and lowest in psychiatry. Hypothesis 2: When comparing by provider types, Vitality scores in the SF-36 scale will be the highest in primary care and care coordination and lowest in psychiatry.

   b. Hypothesis 3: When comparing by provider types, Social function scores in the SF-36 scale will be the highest in primary care and psychiatry and lowest in care coordination.

c. Hypothesis 4: When comparing by provider types, Role Emotional scores in the SF-36 will be the highest in primary care and care coordination and lowest in psychiatry.

d. Hypothesis 5: When comparing by provider types, Mental Health scores will be the highest in primary care and care coordination and lowest in psychiatry.

5. How does the study population's genetic phenotype (poor metabolizer, intermediate metabolizers, ultra-rapid metabolizer) in all provider types compare to the general population genetic phenotypical frequency rates?

Summary of study changes

This study evaluated the provider types of care coordination, primary care and psychiatry providers, changes in depression severity (PHQ9), depression symptoms (QIDS-SR16) and quality of life (SF-36) over time after having pharmacogenetics testing. Data from three studies were combined in a population of patients newly or currently treated for MDD or DDNOS. All participants had a personalized pharmacist's guided report based on their current medications and genetic testing. The similarities of the three studies in patient population, questionnaire completion and timing of visits were similar to allow comparisons between patients managed by each of the three provider types.

Literature Review

This review will provide a brief summary of the literature found to support the need for this study. The purpose of this study was to evaluate by provider types of care coordination, primary care and psychiatrists, the change of depression (PHQ-9),

depressive symptoms (QIDS-SR16) and quality of life (SF-36) over time in a population of patients diagnosed with MDD or DDNOS not in remission after having had pharmacogenetic testing. The following topics were explored in this literature review including depression as was related to the following areas; the prevalence, characteristics in primary care and psychiatry practices, and care coordination and quality of life.

Depression

Worldwide 350 million people suffer from depression, and in the United States, the number suffering from depression is approximately 40 million (World Health Organization, 2015). This number represents primarily women and is the cause of approximately 800,000 suicides every year (World Health Organization, 2015). Pratt and Brody (2008) note that depression varies by socioeconomic status, age, sex and race. Regarding socioeconomic status, those who fell below the federal poverty level and were women age 40-59 had the highest incidences of depressive episodes (Pratt & Brody, 2008). Depression causes functional changes in one's ability to perform daily activities, get along with others and work (Pratt & Brody, 2008). *The Diagnostic and Statistical Manual of Mental Disorders-Revised 5th edition* criteria includes the notation of positive indicators of five out of nine symptoms such as depressed mood, decreased interest or pleasure, changes in weight, changes in sleep, changes in activity, increased fatigue, increased guilt, changes in concentration and suicidality (American Psychiatric Association, 2013). Additionally, poor quality of life has been shown to be associated with depression and reported to be an important factor related to understanding depression (Bonicatto, Dew, Zaratiegui, Lorenzo, & Pecina, 2001; Doraiswamy, Khan,

Donahue, & Richard, 2002; Papakostas et al., 2004; Saarijarvi, Salminen, Toikka, & Raitasalo, 2002; Trivedi et al., 2006)

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A literature review was conducted using the terms 'depression' and 'psychiatry or psychiatric or mental health' and 'primary care', through EBSCOhost with all databases chosen, which yielded 2,668 articles. Limiting the search to full-text, and between the dates of 2010-2016, the number of articles resulted in 732. Topics of maternal mental health, perinatal mental health, child *.*, and veterans were excluded, 552 articles were returned. From these articles three sentinal articles were identified which totaled 13 articles reviewed.

Many studies identify a need to meet evidence-based standards in primary care and a need to improve training in primary care (Mechanic, 2014). The literature search was rich with articles regarding primary care and its ability to identify patients (Lemelin, Hotz, Swensen, & Elmslie, 1994), screen (Tiemens, VonKorff, & Lin, 1999), treat and refer to psychiatry (Ferguson, 2000). Indirect comparisons of provider types have reported that specialty care was more expensive but most effective in treating depression (Sturm & Wells, 1995). One study, which lacked sample size, showed significance toward the superiority of primary care to specialty care for treatment of depression (Scott & Freeman, 1992). Direct comparisons of primary care and psychiatry have been conducted in regard to depression severity and outcomes (Gaynes et al., 2005; Gaynes et al., 2007; Howland, 2008; Rush, 1993; Simon et al., 2001), and medication prescribing (Mayor, 2015).

The earliest comparisons of primary care and psychiatry patients indicate that initial depression severity and number of medical diagnoses were similar in both provider types (Simon et al., 2001). This study also concluded that over time both primary care and psychiatry patients had improvement in their depression and quality of life scores, but there were not any differences between them (Simon et al., 2001). Also, it was observed that there were deficiencies in patient care by both groups, as exampled by poor follow-up with providers. Furthermore, this study added that more care management options would improve patient compliance (Simon et al., 2001). In fact, a study completed earlier identified that when a patient has systematic follow-up from a care manager, depression did improve (Simon & Ludman, 2000). However, a comparison of care management such as care coordination to both primary care and psychiatry has not been reported.

Two recent studies published by Gaynes et al. (2005); Gaynes et al. (2007) assessed the differences in those patients who sought treatment management by a primary care provider or by a psychiatrist. These studies had similar results to Simon et al. (2001), reporting that the depression severity between the two groups was similar. However, the study by Gaynes et al. (2005) indicated that those patients who were managed by psychiatrists had a higher incidence of suicidal ideation and past suicide attempts compared to primary care. In the 2005 study by Gaynes et. al, primary care patients were also less likely to self-select having a depressed mood and anhedonia. The next study Gaynes et al., (2007) conducted included 1,000 more participants and asked similar questions. This subsequent study confirmed findings of equal depression severity, and depression symptom distribution in both primary care and psychiatry groups

(Gaynes et al., 2007). However, when suicide was assessed, it was also found to be equal in both groups for suicide attempts and suicidal ideation, which contradicts the previous report that psychiatry had higher suicide rates (Gaynes et al., 2007)

Care coordination and depression

Literature reviews of EBSCOhost with all databases chosen for the words 'care coordination', and 'depression' returned 377 articles. When children and veterans were excluded 199 articles were returned and 'health to home' was added a return of 7 articles which were unrelated to the dissertation topic were returned. Limiting to full-text available and peer review, decreased the 199 articles to 100. No studies were identified specifically indicating depression care in care coordination. Some topics revealed 'case-management', 'stepped-care', 'collaborative models'. Searches of these and article bibliographies such as from the American Nurses Association and the Institute of Medicine discussions regarding care coordination, 17 articles for this review were identified. Because few results returned articles specific to care coordination, case-management or care management will also be discussed.

While case-management is slightly different than care coordination, case-management provides information regarding improving outcomes for patients associated with guidance within the health care system (Gensichen et al., 2013). Collaborative Care is another model using professional collaboration, evidence-based protocols and has a focus on long-term outcomes of patients with chronic conditions (Gunn et al., 2012). Case-managers can be master's prepared nurses, who orgainize and coordinate care services to maintain continuity of care and minimize costs . Care coordination has many more definitions identified and encompases more scope than case-management

(McDonald et al., 2014; McDonald et al., 2007; Schultz, Pineda, Lonhart, Davies, & McDonald, 2013). Because of the large overlap of practice and extreme similarities between case-management and care coordination, case-management was included in the literature review.

Ekers et al. (2013) conducted a meta-analysis of published studies which used collaborative care model to evaluate its effectiveness in managing patients with depression. This meta-analysis evaluated the results of 14 randomized studies and reported that patients who are managed by nurses and have long-term chronic illnesses have better outcomes than without nurse management (Ekers et al., 2013). Another study showed improvements in depression-free-days when case-management for depression was used in small practice settings (Gensichen et al., 2013). A more recent study of care management for depression, found that patients involved in collaborative depression care had decreases in depression, were compliant with visits, medication, and follow-up with providers better than those who were not followed by care management (Palmer, Vorderstrasse, Weil, Colford, & Dolan-Soto, 2015).

Care coordination was established in the 1990's as a model used in several settings, such as health maintenance organizations (HMO's), and the Centers for Medicare & Medicaid (Craig, Eby, & Whittington, 2011). Care coordination is essential to providing quality care for individuals with complex medication regimens, medical histories, and chronic disease. Plus it is effective for medical and cost outcomes (American Nurses Association, 2012). Nursing has been integral in providing evidence of the effectiveness of care coordination programs, such as care transitions to reduce rehospitalization , and effective coping to manage social issues of homelessness or food

insecurities (Coleman, Parry, Chalmers, & Min, 2006; Craig et al., 2011). Regarding mental health care coordination, studies have shown that telephone contacts to follow up with patients, increase adherence to medication and follow-up appointments (Dietrich et al., 2004; Oxman, Dietrich, Williams, & Kroenke, 2002).

Currently, the Centers for Medicare & Medicaid have a funded project to implement care coordination in care transitions of behavioral health to evaluate rehospitalization because of depression (Gold & Becker, 2015). A report published since this announcement, documents that those patients hospitalized for serious mental illness who participated in the care transitions program, had better follow through rates with their primary care providers than their mental health providers after hospitalization (Domino et al., 2016). This Domino et al. (2016) report indicates a close tie to primary care, and deficiencies in communication with specialty providers.

A comparison of care providers may be helpful to identifing interventions to care for patients with depression. Care coordination programs have been supported by the American Nurses Association and a white paper describes the pivotal, and important role that nursing makes in this program (American Nurses Association, 2012). Care coordination has shown improvements for patient's quality of care, ability to decrease costs, and improve survival rates. Yet, in a literature search, no studies were identified that compared care coordination with primary care or psychiatry providers.

Depression and quality of life

A search for the term "depression" and "quality of life" on EBSCOhost with all databases chosen, yielded 54,405 articles. Limiting it to peer-reviewed scholarly articles, full articles available and reducing the years from unlimited to the last three years, the

result were 15, 754. When the terms "pharmacogenetics" was added, two articles were returned which were not supportive to this dissertation. When the same search of the three terms was conducted in PubMed, 13 articles were returned, three were disregarded because they were duplicates. From these articles bibliographies, and bibliographies of other identified articles, the following review included 10 articles.

Quality of life includes three main components, physical functioning, social functioning, and emotional functioning (Ware, Kosinski, & Keller, 1996; Ware & Sherbourne, 1992a). It is well established that a poor depressive prognosis is associated with poor quality of life (Bonicatto et al., 2001). In a study of depressed persons, it was reported that those who were depressed reported a forty percent impairment in quality of life when compared to those who are not depressed (Ishak et al., 2013). Factors significantly contributing to decreases in quality of life in the depressed population may be associated to depressive symptomology, disability, and age (Ishak et al., 2013).

Depression has an impact on not only mental quality of life but physical functioning, perceived bodily pain and a person's feelings of general wellness (Saarijarvi et al., 2002). The SF-36 evaluates eight domains that make up overall quality of life. These include; physical functioning (PF), physical limitations because of health problems (RP), physical, body pain (BP), general perceptions regarding health (GH), vitality (VT), social functioning (SF), limitations due to social or emotional problems (SE), and mental health (MH) (McHorney, Ware, & Raczek, 1993).

Bonicatto et al. (2001) reported poorer quality of life in persons with depression than those with or without chronic conditions, which indicates the extent of the impact depression may have on health outcomes. Similar results were found in an elderly

population noting that quality of life in depressed persons was at least as debilitating as a chronic physical condition (Doraiswamy et al., 2002). Additionally, as age increases, physical quality of life decreased. Interestingly, the elderly tended to have higher scores overall on the quality of life measure indicating that with age people are more content overall (Doraiswamy et al., 2002). Understanding the impact of physical health to mental health can give a more impactful view of depression and its treatments (Ishak et al., 2013). Not all studies report positive outcomes for those with improvement in depression. One study reported that only fifty percent of patients who were in remission for depression, improved quality of life scores (IsHak et al., 2015).

Physical quality of life has been recently evaluated in bipolar participants of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study to examine the relationship of physical quality of life and bipolar symptoms. The analysis revealed that Role physical and General Health scores within the Short Form 36 survey were related to and predicted worsening depression. Also, those who reported fewer depressive symptoms had fewer physical limitations (Bernstein et al., 2016). The impairment in quality of life for persons with depression and the additional impact on physical health indicates a need to understand physical symptoms associated with depression in addition to quality of life (Ishak et al., 2013). Having chronic conditions could explain why those with remission of depression continue to have decreased quality of life scores (Alonso et al., 2004).

The literature review reveals that more research is needed in the use and effectiveness of a locally developed multi-gene assessment to guide provider pharmacotherapy prescribing. Also, when considering other published studies that

include a comprehensive pharmacogenetic report related to psychotropic medications, it is interesting to note that quality of life has not been addressed (Altar et al., 2015{Hall-Flavin, 2013 #242). The STAR*D literature indicates the need for quality of life assessment to more fully understand patients and their depression symptoms (Trivedi et al., 2006).

Theoretical Framework

The theoretical framework for this new study had no changes from the previous study and is as described in chapter one and two.

Nursing theory

The nursing theory used was Orem's Theory of Self-care. This is unchanged from Chapter one and two. The new model appears below in Figure 5. This illustrates changes in depression severity, depression symptoms and quality of life without regard for provider type. However, the awareness of having pharmacogenetic care, may impact a patient outcome positively. Some authors have indicated that this is a placebo effect (Haga, Warner, & O'Daniel, 2009)

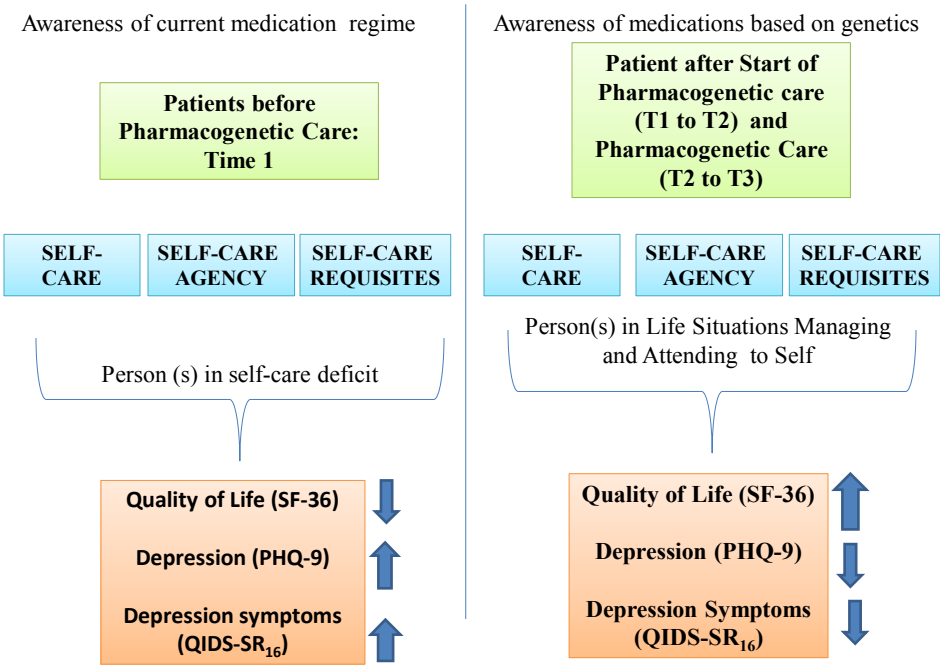

Figure 5. Depression severity (PHQ9), depression symptoms (QIDS-SR$_{16}$), and quality of life (SF-36), as they are associated to Self-care deficit.

Study significance

In consideration of providers, nurse prescribers, and other professions working with patients, opening communication between the provider and patient because of pharmacogenetic testing may increase patient's quality of life, and decrease depression severity and symptoms. Furthermore, increases in quality of life may promote patient's active participation in self-care behaviors, decrease missed clinic visits and promote the intentional and appropriate use of resources. Few differences have been identified between primary care and psychiatry in studies to date. However, indications that managed care may be beneficial to depression outcomes can be evaluated through a comparison of care coordination to primary care and psychiatry. Current literature was not identified that show evidence of what differences might be found between these

populations. The American Nurses Association (2012) provides primary evidence to the impact that nursing can make on the outcomes of patients who are participating in care coordination. Nursing is poised for providing interventions which may be helpful to care coordination participants with depression.

Methods

The purpose of this dissertation study was to evaluate by provider types of care coordination, primary care and psychiatry, the change of depression severity (PHQ-9), depressive symptoms (QIDS-SR16) and quality of life (SF-36) over time (T1-T3) in a population of patients diagnosed with MDD or DDNOS after having had pharmacogenetic testing. The methods section will discuss study design, population, study data collection, instruments used, and statistical analysis.

Study Design

This study was an analysis of data from three similar studies evaluating MDD and DD-NOS. The data from these three studies were combined. All of the studies utilized a prospective, repeated-measures design and two of the studies were randomized prospective repeated-measure designs.

Sample and Setting

This study was conducted in collaboration with a large health care system, clinics, and hospitals in the upper Midwestern United States. The health system covers over 70,000 members in three states, and there are over 300 facilities within the health system. This study focused on participants in three studies of pharmacogenetics in patients who had a diagnosis of depression and who had completed three visits. The three key visits

analyzed included a baseline visit (T1), a visit at pharmacogenetics reporting (T2), and a visit after pharmacogenetic report (PGXr) has been given to providers (T3). If the subject were in a study that had randomized pharmacogenetics results given to the provider at 12 weeks, the same data collection points would be utilized. However, there would be different time intervals between data collection points. For example, a patient who is randomized to "twelve-week reporting", will receive a pharmacogenetics report eight weeks after the patient who is randomized to "four-week reporting" (Table 4)

Table 5

Three study randomizations

Primary care and Specialists care: RANDOMIZED TO 4 WEEKS						
weeks	0	4	8	12	16	18
Time point evaluated	*T1	*T2	*T3			
Visit Number	V1	V2	V3	V4	V5	V6
PHQ9	x	x	x	x	x	x
QIDS-SR16	x	x	x	x	x	x
SF-36	x	x	x	x	x	x
PGXr (randomized to 4 or 12 weeks)		x		x		
				**data not utilized for this analysis		
Primary care and Specialists care: RANDOMIZED TO 12 WEEKS						
weeks	0	4	8	12	16	18
Time point evaluated	*T1			*T2	*T3	
Visit Number	V1	V2	V3	V4	V5	V6
PHQ9	x	x	x	x	x	x
QIDS-SR16	x	x	x	x	x	x
SF-36	x	x	x	x	x	x
PGXr (randomized to 4 or 12 weeks)		x		x		
Care Coordination study: had no randomization						
weeks	0	4	8	12	16	18
Time point evaluated	*T1	*T2	*T3			
Visit Number	V1	V2	V3	V4	V5	V6
PHQ9	x	x	x	x	x	x
QIDS-SR16	x	x	x	x	x	x
SF-36	x	x	x	x	x	x
PGXr		x				

*Time points evaluated for this study.

Population

The sample population included participants in three studies of depression and the criteria for this analysis included the following:

Inclusion criteria

1. The participant had a diagnosis of MDD or DDNOS.

2. The participant had completed informed consent for the study in which they were enrolled.
3. All participants in the study were evaluated regardless of how many visits they had completed.
4. The provider managing the patient's depression (primary care or specialist) consented to the patient's participation in the study.
5. Participants were 18 years old or older, males or females.
6. Participants were taking, or the provider planned on starting, an antidepressant medication to be included in the study.
7. Participants who had a history of substance abuse, other than nicotine, had to be stable in the opinion of the principal investigator and provider.
8. Participants had a life span expectancy of a year or longer.
9. Subjects must have been able to read and write in English.

Exclusion criteria. All patients met the exclusion criteria to participate in the dissertation research.

1. Participants were not pregnant or breastfeeding mothers.
2. Participants were not younger than 18 years old.
3. Participants did not have a primary diagnosis of Dementia, bulimia, or anorexia nervosa disorder diagnosis.
4. Participants who had a previous pharmacogenetic evaluation were excluded.
5. Participants who had disorders affecting drug absorption (i.e., Crohn's Disease or Colitis, significant surgical procedures affecting medication or food

absorption, or conditions as identified by the principal investigator to interfere with medication absorption).

Recruitment. Recruitment was described in the "care coordination" dissertation chapters' methods section. Recruitment for those in the 'primary care provider' or the 'specialists (psychiatry) studies occurred through provider referral to the study staff of those studies. Primary care participants were recruited from various clinics and hospitals throughout the health system, and all study visits were completed over the phone. Questionnaires were mailed to participants and follow-up phone calls made as needed. The specialists (psychiatry) study participants were referred by their psychiatrist and were seen in the psychiatrist's office. All questionnaires for these patients were completed in person at the psychiatry office.

Study Schedule. For this study regardless of randomization, the study visits assessments included the baseline, the visit at which the PGXr was given to the provider, and one month after the pharmacogenetics report was received (Table 3 and 4)

Data Collection

Instruments

Patient Health Questionnaire-9 (PHQ9). The PHQ9 is a 9-item, self-report measure of depression severity, scored from zero to 27. Each of the nine questions have four answer options (0-3) defining the severity and, or frequency of symptoms over the past two weeks; zero denotes 'no symptoms at all'. A score of 1 represents symptoms are experienced 'several days', and a 2 indicates that symptoms are experienced 'more than half the days'. The highest score, 3, signifies 'nearly every day' symptoms are experienced. The instrument evaluates the previous two weeks. PHQ9 scores ranging

from 0-4, were minimal depression, 5-9 indicate mild depression, 10-14 represent moderate depression, 15-19 designate moderately severe depression and more than 20 designates severe depression (Kroenke, Spitzer, & Williams, 2001; Manea, Gilbody, & McMillan, 2011).

When the PHQ9 was evaluated and compared to independent physician diagnosis, it was found to be accurate at 85%, have 90% specificity, with a sensitivity of 90% (Spitzer, Kroenke, & Williams, 1999). The PHQ9 has a reported Cronbach's alpha of 0.85 indicating good internal reliability, and Spitzer et al. (1999) reported criterion validity based on the concurrence of diagnoses indicated by individual providers compared to the PHQ9. Construct validity was strong when SF-20 was compared to PHQ9 measurement indicated that as PHQ9 scores rise, patient's functional status decreases on the SF-20.

Quick Inventory of Depressive Symptomology-Self Report 16 (QIDS-SR16). The QIDS-SR 16 was developed from a 30 Item Inventory of Depressive Symptomology (IDS30) to decrease the length and develop a self-report scale and clinician's rating scale (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996; Rush et al., 2003). This scale was evaluated against the Hamilton Depression Scale ($HAMD_{24}$) which has (Cronbach's alpha = 0.88) high internal consistency (Rush et al., 2003). The internal consistency of the QIDS-SR_{16} was also found to be high (Cronbach's alpha = 0.92), and total scores are predictive of $HAMD_{17}$ scores by multiplying 1.3 times the total QIDS-SR_{16}. Additionally, high relative validity has been established with other instruments including the HAMd24, HAMD17, QIDS30, and MADRS (Carmody et al., 2006). A comparative table is available for HAMD24, HAMD17, and QIDS30 (Rush et al., 2003).

The QIDS-SR_{16} is a self-report tool which evaluates nine domains including a) sad mood; b) concentration; c) self-criticism; d) suicidal ideation; e) interest; f) energy/fatigue g) sleep changes including initiation of sleep, middle and late insomnia or hypersomnia; h) increased or decreased appetite/weight; i) psychomotor agitation/retardation. Each domain has two to three questions associated with it for a total of sixteen questions. Each of the nine items is scored with a value given from 0-3 for each answer. The highest item score within a domain is chosen as the final score for that domain. The total scores for the nine domains may range from zero to twenty-seven. Twenty-seven reflects the most severe symptoms related to depression. Mild depression is scores of six to ten, 11-15 is moderate, 16-20 is severe and more than 21 is very severe depression (Rush et al., 1996; Rush et al., 2003; Trivedi et al., 2004).

Short Form 36 (SF-36) Health Survey. The Short Form-36 (SF-36) Health Survey for measuring quality of life, was developed to understand health outcomes in population health, clinical health initiatives, and research in many different disease states that include pain, cardiovascular disease, cancer and psychiatric diagnoses as some of the most prolific uses. It has been widely published with over 4,000 publications using this instrument to measure health outcomes (Turner-Bowker, Bartley, & Ware, 2002).

The quality of life measure, the SF-36 is a 36 item self-report instrument, using both five-point and 3 point Likert scales. The five-point scale goes from a score of zero to five, zero being severe symptoms and five being no symptoms. The three-point scale is used, for example, when asked about physical limitations and zero indicates 'yes, limited a lot' while three indicates, 'not limited.' All subscales are scored from zero, which is severe symptoms to 100 which is no symptoms. The subscales are combined

and averaged to create a 'physical composite score' and a 'mental composite score'. A zero represents poor quality of life, to 100 which is high quality of life. The higher the score, the better quality of life is observed by participants. McHorney et al. (1993); Ware et al. (1996); Ware and Sherbourne (1992a) explain the eight domains of health including; 'physical functioning' (PF), physical limitations because of health problems- 'role physical' (RP), physical, 'body pain' (BP), general perceptions regarding health- 'general health' (GH), 'vitality' (VT), 'social functioning' (SF), limitations due to social or emotional problems 'role emotional' (RE), and 'mental health'(MH). The 'mental composite score' (MCS) and the 'physical composite score' (PCS) are averages of four related subscales. The MCS includes PF, RP, BP, and GH. The PCS includes VT, SF, RE, and MH. The two scores which are commonly used are the PCS and MCS (Ware & Sherbourne, 1992b). Each domain and meanings of each domain and what they represent are presented (Table 6). Frendl and Ware (2014) evaluated pharmaceutical clinical studies that utilized the SF-36 and noted that there were significant changes in scores in several disease states, the top being rheumatoid arthritis, and psoriasis. Depression was also noted to have good responses for changes in the SF-36 after beginning medication, which confirms the usefulness of the SF-36 in clinical trials utilizing drug therapy (Frendl & Ware, 2014).

Table 6

SF36 subscales	**Low Scores (0 - 50)**	**High Scores (> 50)**
Physical Composite Score		
physical functioning	Unable to complete activities of daily living	Completes activities of daily living without limitations
role-physical	Physical health interferes with work or job activities	Physical health does not interfere with work activities
Bodily pain	Severe pain	mild to no pain
General Health	Has the belief that health will become worse	Has the belief that health will improve
Mental Composite Score		
Vitality	Low energy levels	Has energy and pep
Social Function	physical or emotional problems interfere with social life	There are no social life limitations because of either emotional or physical problems
Role-emotional	Emotional problems interfere with work or job activities	No work or job interferences because of emotional problems.
Mental Health	Anxiety or sadness most of the time	Feels happy and relaxed most of the time.

Ware and Sherbourne (1992a, p. 475)

Number of chronic conditions and mental health conditions. The number of chronic conditions and mental health conditions was a tally of diagnoses, one number for a chronic condition and one number for mental health conditions as listed in the patient's medical record and associated with an ICD-9 or ICD-10 code.

Demographic Information. Age, gender, type of medical insurance, marital status, and employment status were collected.

Statistical Analysis

Sample size estimate. Sample size was based on recruited patients up until January 2016 when the study was stopped. Original sample size estimates were 100 per study based on the G*POWER sample size calculator. The statistical plan is represented below (Table 7).

Table 7

Statistical plan

Hypothesis	Variable	Type of Variable	Comparison	Statistical Test
1	PHQ9 - Dependent	discrete variable (nominal)	PHQ9 at T1, T2, T3	mixed linear models
2	QIDS-SR Dependent	continuous/interval/ratio	QIDS-SR at T1-3	mixed linear models
3	QOL-Mental Health dependent	continuous/interval/ratio	QOL-MH at T1, T2, T3	mixed linear models/ Jonckheere-Terpstra
4	QOL physical health dependent	continuous/interval/ratio	QOL-PH at T1, T2, T3	mixed linear models/Jonckheere-Terpstra
5	Genetics	descriptive statistics (frequencies)		

T1 = Time 1, T2 = Time 2, T3 = Time 3

Data analysis. Data was entered into SPSS® v.22, and double checked by two additional staff persons. A master file copy was saved, and password protected as backup for the working file. A working file copy was made to conduct the analysis. Additionally, initial checks for outliers and frequency distributions, boxplots, histograms and descriptive statistics were conducted. Data analysis included the mixed linear model. This model is helpful to use with data such as is presented here, which has missing variables, and inconsistent group sizes (Field, 2013).

CHAPTER 4

Results

The purpose of this dissertation study was to evaluate by provider types of care coordination, primary care and psychiatry, the change of depression severity (PHQ-9), depressive symptoms (QIDS-SR16) and quality of life (SF-36) over time (T1-T3) in a population of patients diagnosed with MDD or DDNOS after having had pharmacogenetic testing. This chapter describes the data collection, cleaning, and analysis methods and results for each question.

Review of Data Collection Procedure

Summary of study procedures and study sample. Data was collected from three ongoing studies of pharmacogenetics in depression. All patients had a diagnosis of Major Depressive Disorder (MDD), or Depressive Disorder- Not otherwise specified (DDNOS). All participants completed the same questionnaires including the PHQ9 to measure depression severity, the QIDS-SR to measure depression symptoms, and the SF36 to measure quality of life.

Each study sought to enroll 100 volunteers per provider type. At the time of this analysis, 100 participants had not yet been achieved for each study. Data collected through February 6, 2016, was combined to complete this analysis and included populations with the differing provider types of care coordination (n = 26), primary care (n = 38), and psychiatry (n = 54). All participants were included in the analysis who had signed informed consent for their study regardless of how many visits the participants had completed. Two of the studies, primary care and psychiatry, were randomized studies. The study visits were standardized, so that regardless of randomization, the same time points were evaluated. Evaluation of a baseline visit, the visit which the participant

received their pharmacogenetics report (PGXr) and one visit four weeks after receipt of the PGXr were collected for data analysis.

Data collection challenges included missed visits, due to patient non-compliance and missed visits related to the visit number which the participant was currently completing at the time the study closed enrollment. Some participants were newly enrolled and only finished one visit while others had completed the entire study at the date of the data analysis.

Questionnaire data was manually entered into a Microsoft Excel spreadsheet for each study. After manual entry, data was double-checked by an independent researcher. Data was source verified, de-identified and cleaned for analysis. All data was password protected, and analysis was completed in SPSS® v. 22.

Statistical Methods. Descriptive statistics were implemented for data analysis of the populations. These included frequency, means (*M*), standard deviations (*SD*), medians, and sample size counts. This information was used to understand missing values, and distributions of the data. T-tests were conducted for comparison of groups; Bonferroni corrections were made when multiple t-tests were completed.

A mixed linear model was used to analyze the repeated measures of depression severity (PHQ9), depression symptoms (QIDS-SR16), and quality of life (SF36). Mixed linear model was chosen over ANOVA for repeated measures because of the number of missing values, and missed visits (Bernstein et al., 2010). Mixed linear models are more robust in analyzes when there are missed visits, which may interfere with sample size (Hardin & Hilbe, 2012; Heritier, 2009). Mixed linear models provide information regarding the data in a multilevel evaluation of repeated measures such as are represented

in this study. This model provided information regarding between and within group effects. Schwarz's Bayesian Criterion was evaluated for p values of each model selected. The validity of each model utilized having a p-value < .05, was tested against variations of the final statistical model. To understand detailed trends and rank between groups and time periods for the quality of life criteria (SF36), the Jonckheere-Terpstra trend statistic, a non-parametric test, was used for the concepts included in the 'mental composite scores' (MCS) and 'physical composite scores' (Jonckheere, 1954) for more information regarding the subscale concepts, refer to the table (Table 5).

Internal reliability for questionnaires

A Cronbach's alpha was calculated for each questionnaire used for this study and showed good reliability as > 0.70 for all questionnaires used. The PHQ9's Cronbach's alpha was .88, which was slightly higher than the reported .85 of previous studies. The QIDS Cronbach's alpha was .76, which was lower than previous reports of .88 -. 92. The SF-36 has two measures, physical composite score (PCS) and mental composite scores (MCS), which were Cronbach's alpha was .97 and .89 respectively. The SF36 subscale Cronbach's alpha for both primary scores of MCS, and PCS ranged from .79 to .94. The SF-36 internal reliability measures were similar to previously reported Cronbach's alphas.

Demographic results

Sample Demographic results. The sample population participated in three studies conducted in the upper Midwest. The studies included patients who were referred by their providers including primary care, and psychiatric providers along with care

coordination referrals. Tabular demographic results are represented (Table 8) and clinical demographics are also presented (Table 9).

Table 8

Demographic distribution

		n =	*%*
Gender *N* = 124	Male	31	24%
	Female	93	73%
Ethnicity *N* = 117[a]	Caucasian	115	90%
	Unknown	1	1%
	American Indian	1	1%
Employment Status *N* = 124	Employed	46	37%
	Unemployed	7	6%
	Retired	6	5%
	Disabled	10	7%
	Unknown	55	43%
Marital Status *N* = 117[a]	Single	39	32%
	Married	59	48%
	Divorced	16	13%
	Separated	0	0%
	Widowed	3	2%
Insurance Type *N* = 124	Private	83	65%
	Self-pay	4	2%
	Medicaid	37	30%
Smoking status *N* = 121[b]	Non-smoker	74	61%
	Current smoker	17	14%
	Former smoker	19	16%
	Unknown	11	9%

a. Missing data (n = 7) *N* = 124.
b. Missing data (n = 3) *N* = 124.

The total sample size was *N* = 124, with ages ranging from 19 to 84 years old (*M = 45*, *SD = 14.66)*. The overall sample was Caucasian (90.3%) and female (73.4%). In

addition, the majority of the population was employed (37.1%) with private insurance (65.3%), and fewer participants were unemployed (4.6%), retired (4.8%) or disabled (7.3%). Similarly, fewer participants had Medicaid (29.8%) or were self-pay (2.4%). Most participants were married (47.6%) followed by less who were single (31.5%). There was a wide range (0-17) of number of chronic conditions.

Table 9

Total Sample Descriptive Statistics

	N	Minimum	Maximum	*M*	*SD*
Age	120	19	84	45.69	14.67
Number of chronic illnesses	118	0.00	17.00	4.37	3.90
Number of mental health diagnoses	118	1.00	6.00	2.08	1.18
Number of medications	115	0	37	10.64	7.17

Demographics based on provider type. The demographics by provider included, care coordination (*n* = 24), primary care (*n* = 41), and psychiatry (*n = 54).* The demographics information gathered during the study included: a) age b) gender c) primary health insurance d) marital status e) ethnicity, d) employment, e) number of chronic health conditions f) number of mental health conditions. Primary health insurance was categorized as self-pay, Medicaid, or private insurance. Employment was classified as employed, unemployed, disabled, retired or unknown. Marital status was classified as single, married, divorced, separated, or widowed. Clinical demographic descriptive statistics were conducted on these data (Table 9).

Table 10

Demographics by provider type

Sample Characteristic		Care Coordination	Primary Care	Psychiatry
Sample size		n = 26	n = 41	n = 54
		%	%	%
Gender	Female	73.1	80.5	72.2
	Male	26.9	19.5	27.8
Ethnicity	Caucasian	92.3	87.8	96.3
	Unknown	3.8	12.2	3.7
	Native American	3.8	0.0	0.0
Insurance Type	Private	30.8	75.6	77.8
	Self-pay	3.8	0.0	3.7
	Medicaid	65.4	24.4	18.5
Employment Status	Employed	38.5	26.8	46.3
	Unemployed	3.8	9.8	3.7
	Disabled	23.1	0.0	5.6
	Unknown	34.6	61.0	35.2
	Retired	0.0	2.4	9.3
Marital Status	Single	38.5	36.6	25.9
	Married	42.3	51.2	46.3
	Divorced	19.2	4.9	14.8
	Widowed	0.0	2.4	3.7

Table 11

Clinical demographics by provider type

	Care coordination	Primary Care	Psychiatry
	M (SD)	*M (SD)*	*M (SD)*
Age	50.38 (11.19)	44.10 (15.01)	44.61(15.62)
Number of chronic conditions	7 (3.5)	3.52 (4.17)	3.7 (3.32)
Number of mental health diagnoses	2.15 (1.54)	2.12 (1.07)	2.0 (1.07)
Number of Medications	15.04 (6.83)	8.62 (6.22)	9.88 (7.16)

n = 4 missing data for age, n = 6 missing data for number of chronic illnesses and number of mental health diagnoses, n = 9 missing for number of medications. *N = 124*

Age. Age was compared for three groups, care coordination, primary care and psychiatry. Groups were similar p = 0.149, at a significance level of p = .05. The mean age among groups, were care coordination (*M* = 50.38, *SD* = 11.19), psychiatry (*M* = 44.61, *SD = 15.62*) and primary care (*M* = 44.10, *SD = 15.01*).

Gender. The total sample for all groups included 32 males and 94 females. The proportions in gender between groups were similar; care Coordination (73.1%), primary care (80.5%) and psychiatry (72.2%).

Insurance type. Private insurance was the primary insurance type for both primary care and psychiatry (n = 31; n = 42). Medicaid was the primary insurance type for care coordination with (n = 17).

Marital status. This study's total population included the largest percent who were married (47.6%) over those who were single (31.5%). Similarly, Table 10 shows that each group has a high number of married and single participants. Care coordination, primary care, and psychiatry all had the high percentages of people whose status was

married, 42.3%, 51.2%, 46.3% respectively. Care coordination had the highest percentage of divorced and single participants 19.2% and 38.5% respectively.

Employment. Primary care, care coordination and psychiatry groups had the following rates of employment, respectively from 26.8%, 38.5%, to 46.3%. Care coordination had the highest percentage of disabled participants (23.1%), and psychiatry had the highest percentage of retired participants, 9.3%.

Number of chronic conditions. There was a difference ($p < 0.001$) in chronic physical conditions between care coordination, ($M = 7.0$, $SD = 3.5$), primary care ($M = 3.52$, $SD = 4.169$) and psychiatry ($M = 3.7$, $SD = 3.32$).

Number of mental health diagnoses. There was no difference among groups for the number of mental health diagnoses ($p = 0.801$).

Number of medications. Care coordination patients were prescribed more medications than primary care ($p = .001$), and psychiatry groups ($p = .006$). There was no difference between primary care and psychiatry groups ($p = 1.00$).

Analysis of group for depression severity (PHQ-9)

Table 12

PHQ mean scores all patients

				95% Confidence Interval for Mean	
Visit	*n*	*M*	*SD*	Lower Bound	Upper Bound
1.00	120	14.6000	5.50080	13.6057	15.5943
2.00	99	11.7879	5.78223	10.6346	12.9411
3.00	90	10.2444	6.26263	8.9328	11.5561
Total	309	12.4304	6.08483	11.7493	13.1115

The mean depression severity scores decreased over time $F (2, 303) = 15.3l$, $p = .001$. There was a decrease in score from visit one ($M = 14.6$, $SD = 5.5$) to visit two ($M =$

11.78, *SD* = 5.7), with a mean decrease *M* = -2.8, 95% CI [-4.7, -.91], which was statistically significant (*p* = .001). Table 11 shows means and standard deviations for each visit. There was not a significant decrease from visit two (*M* = 11.79, *SD* = 5.8) to visit three (*M* = 10.2, *SD* = 6.2) with a mean decrease *M* = -1.54, 95% CI [-3.6, .50], which was not statistically significant (*p* = .21). The mean decrease from visit one to visit three was significant, *M* = -4.36, 95% CI [-6.31, -2.40], *p* < .05.

Analysis of group for depression symptoms (QIDS)

Table 13

Mean scores for all participants QIDS

				95% Confidence Interval for Mean	
Visit	*N*	*M*	*SD*	Lower Bound	Upper Bound
1	121	13.10	4.52	12.28	13.91
2	99	12.14	6.98	10.75	13.53
3	92	9.62	5.15	8.55	10.69
Total	312.00	11.77	5.75	11.13	12.41

The mean depression symptom scores decreased over time F (2, 309) = 10.46, p < .001. There was a decrease in mean score from visit one to visit two (Table 13). However, this did not represent a significant change, as represented by a mean decrease *M* = -.96, 95% CI [-2.8, .87], *p* = .62. There was a decrease from visit two to visit three with a mean decrease *M* = -2.5, 95% CI [-4.5, -.57], *p* = .01). The mean decrease from visit one to visit three was significant, *M* = -3.5, 95% CI [-5.3, -1.6], *p* = < .001.

Analysis of group for QOL-physical composite scores

Table 14

SF-36 Mean physical quality of life scores by visit-PCS

				95% Confidence Interval for Mean	
Visit	*N*	*M*	*SD*	Lower Bound	Upper Bound
1	119	43.96	12.36	41.72	46.20
2	90	45.48	12.77	42.81	48.16
3	92	45.75	12.20	43.22	48.27
Total	301	44.96	12.42	43.55	46.37

There was not a change in physical quality of life F (2, 298) = .648, p = .52. The means are represented at each visit (Table 12), and the change in means between visits (Table 14) are also represented.

Table 15

SF-36 multiple comparisons of physical composite score by visit

				95% Confidence Interval	
(I) VISIT		*M* (mean difference)	*p*	Lower Bound	Upper Bound
1	2	-1.52	1.00	-5.71	2.66
	3	-1.79	0.91	-5.94	2.37
2	1	1.52	1.00	-2.66	5.71
	3	-0.26	1.00	-4.70	4.18
3	1	1.79	1.73	0.91	-2.37
	2	0.26	1.84	1.00	-4.18

Analysis of group for QOL-mental composite scores

Table 16

SF-36 mean scores by visit- Mental composite score

				95% Confidence Interval for Mean	
	N	*M*	*SD*	Lower Bound	Upper Bound
1	119	29.97	11.21	27.93	32.00
2	90	35.23	13.01	32.51	37.96
3	92	36.97	12.15	34.46	39.49
Total	301	33.68	12.41	32.28	35.09

There was an increase in quality of mental composite scores, F (2,298) = 9.8, p < .001. (Table 16). A pairwise comparison indicates that there was an increase from visit one to visit two, M = 5.3, 95% *CI* [1.21, 9.3], p < .01 and between visits one and three, M = 7, 95% CI [*2.97, 11.3], p* < .001. However, there was not a change between visit two and visit three, M = 1.74, 95% CI [-2.56, 6.04], p = .993.

Research questions

1. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in depression severity (PHQ9) over time (T1-T3) based on the type of provider?

The statistical model for the PHQ9 included time and provider type as main effects and time and provider interactions (p < .05). The interaction of provider type and time was significant for depression severity, F (2, 102.81) = 3.84, p = .024. Pairwise comparisons indicate that care coordination patients had less severe depression severity, b = -2.501, t = -7.718, p < .001, than primary care and psychiatry patients. In contrast,

there was no difference between PHQ9 scores for primary care and psychiatry in depression severity $b = .499$, $t = .89$, $p = .373$.

a. Hypothesis 1: Depression severity scores (PHQ9) among patients who receive care coordination will decrease over time.

This study found that PHQ9 mean scores (*SD*) decreased with each visit from visit one to visit three respectively, $M = 10.52$, $SD = 6.85$; $M = 10.18$, $SD = 7.60$; $M = 8.11$, $SD = 6.34$. However, this did not represent improvement, $t = 1.195$, $p = .24$. This hypothesis was not supported. Depression severity was represented as changes in patient's depression severity of levels > 9 to levels < 9, indicating clinical improvements (Table 17)

Table 17

PHQ scores	**PHQ-9 (< 8) Low Depression Severity**			**PHQ-9 (≥ 9) High Depression severity**		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Overall Group n = 121						
Number of participants	44	80	94	77	41	27
Percent of participants	36.36	66.12	77.69	63.64	33.88	22.31
Care Coordination n = 26						
Number of participants	16	22	23	10	4	3
Percent of participants	64.54	84.62	88.46	38.46	15.38	11.54
Primary Care n = 41						
Number of participants	12	26	33	29	15	8
Percent of participants	29.27	63.41	80.49	70.73	36.59	19.51
Psychiatry n = 54						
Number of participants	16	32	38	38	22	16
Percent of participants	29.63	59.26	70.37	70.37	40.74	29.63

b. Hypothesis 2: Depression severity scores (PHQ9) among patients who receive care by a Primary care provider will decrease over time.

PHQ9 mean scores decreased with each visit from visit one to visit three, M = 16.0, SD = 4.955; M = 13.73, SD = 5.11; M = 12.0, SD = 5.98. These means indicate a decrease in depression, t = 2.874, p = .006. Twenty-one participants (51%) who were being managed by primary care providers reduced their depression severity scores from being greater than 9 (moderate to severe) to less than 9 indicating a mild depression status (Table 16). This hypothesis is supported.

c. Hypothesis 3: Depression severity scores (PHQ9) among patients who receive care by a Psychiatrist will decrease over time.

PHQ9 mean scores decreased with each visit from visit one to visit three, M = 15.42, SD = 4.25; M = 11.16, SD = 5.33; M = 10.2, SD = 6.22. This indicates a decrease in depression severity from visit 1 to visit 3, t = 4.95, p < .000. Twenty-two participants (41%), reduced their depression severity category by moving from having a score greater than nine at visit one to having a score less than nine at visit three. This hypothesis is accepted.

Table 18

QIDS severity groups	**QIDS-SR (<10) Fewer symptoms**			**QIDS-SR (≥11) More symptoms**		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Overall Group						
Number of participants	48	73	92	73	48	29
Percent of participants	39.67	60.33	76.03	60.33	39.67	23.97
Care Coordination						
Number of participants	16	19	22	10	7	4
Percent of participants	64.54	73.08	84.62	38.46	26.92	15.38
Primary Care						
Number of participants	11	31	30	30	10	11
Percent of participants	26.83	75.61	73.17	73.17	24.39	26.83
Psychiatry						
Number of participants	21	23	40	33	31	14
Percent of participants	38.89	42.59	74.07	61.11	57.41	25.93

2. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in depression symptoms (QIDS-SR16) over time (T1-T3) based on provider type?

Table 19

Type III Tests of Fixed Effects QIDS

Source	Numerator *df*	Denominator *df*	*F*	*p*
Provider	2	118.932	6.929	.001
Visit	1	98.492	34.829	.000
Provider * Visit	2	97.521	3.055	.052

a. Dependent Variable: QIDS.

The statistical model included interaction and main effects of provider type and visit for depression symptoms (QIDS) at the level of $p < .05$. There was no interaction found between provider type and change over time for depression symptoms, F (2, 97.52) = 3.05, $p = .052$. There were main effects of visit and provider (Table 18). The number of participants who moved from high levels of symptoms (QIDS >11) to low levels of symptoms (QIDS <11) are presented above (Table 17). Clinically, this indicates that 36% of patient's symptoms improved from visit one to visit three (Table 17).

a. Hypothesis 1: Depression symptom scores (QIDS-SR16) will decrease over time (T1-3) among patients who receive care coordination.

For care coordination the mean scores declined from $M = 10.5$, $SD = 4.14$ at visit one to $M = 9.0$, $SD = 3.56$ at visit 3. However, visit two increased to $M = 11.6$, $SD = 5.2$. Overall, this did not represent a decrease in symptoms, $t = 1.19$, $df = 15$, $p = .25$. The hypothesis was not supported. Clinically this represents a change from high

depression symptoms (QIDS > 11) to low depression symptoms (QIDS <11) for 23% of patients. This does not support the hypothesis.

b. Hypothesis 2: Depression symptoms scores (QIDS-SR16) will decrease over time (T1-T3) among patients who receive Primary care services.

Visit one $M = 14.8$, $SD = 4.72$, decreased to $M = 9.77$, $SD = 4.63$ at visit two and then increased to $M = 11.0$, $SD = 5.3$ at visit three. This represented a decrease in depression symptoms, $t = 2.9$, $df = 24$, $p = .007$. Clinically this represented a change from high depression symptoms (QIDS >11) to low depression symptoms (QIDS< 11) for 46% of patients. This supports the hypothesis.

c. Hypothesis 3: Depression symptoms scores (QIDS-SR16) will decrease over time (T1-T3) among patients who receive care through psychiatry.

The mean depression symptom scores decreased from visit one to visit three respectively, $M = 13.1$, $SD = 4.0$; $M = 13.64$, $SD = 8.2$; $M = 9.1$, $SD = 5.5$. This represents a decline from baseline assessment to visit three, $t = 5.8$, $df = 47$, $p = .000$. Clinically this represent a change from high depression symptoms (QIDS >11) to low depression symptoms (QIDS< 11) for 35% of patients. This supports the hypothesis.

3. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in the physical composite score (physical functioning, role physical, bodily pain, general health) of the SF-36 scale by provider type?

Table 20

Estimated Marginal Means for PCS by Provider

Provider type	*M*	*SD*	*df*	95% Confidence Interval	
				Lower Bound	Upper Bound
Care Coordination	37.12	2.28	119.69	32.60	41.64
Primary Care	46.10	1.79	120.60	42.56	49.64
Psychiatric Care	47.11	1.56	117.34	44.02	50.20

a. Dependent Variable: PCS.

A one-way ANOVA indicates that care coordination patients had poor physical quality of life compared to both primary care F (2, 116) = 10.38, p = .000 and psychiatry patients, F (2, 89) = 4.38, p = .015. There is no difference between primary care and psychiatry groups, with a mean difference of -1.1, SE = 2.39, p = .646.

Table 21

SF 36 Quality of life, comparison of visit and provider

SF-36 Concept	Visit	Care Coordination (CC) *represented in means*	Primary Care (PC) *represented in means*	Psychiatry (PS) *represented in means*
PCS	1	35.02*	64.44	68.35
	2	*No comparisons made, there were no differences found at this visit.*		
	3	29.33*	48.93	51.74
PF	1	39.02*	66.6	64.78
	2	*No comparisons made, there were no differences found at this visit.*		
	3	30.64*	50.77	50.11
RP	1 & 2	*No comparisons made, there were no differences found at this visit.*		
	3	35.92*	43.82	52.27
BP	1	41.46*	62.15	67.08
	2	*No comparisons made, there were no differences found at this visit.*		
	3	31.69*	47.59	51.63
GH	1-3	*No comparisons made, there were no differences found at this visit.*		
MCS	1	91.96*	49.26	53.24
	2 & 3	*No comparisons made, there were no differences found at this visit.*		
VT **SF** **RE**		There were no differences in VT, SF, RE at any visit.		
MH	1	86.24	54.06	52.22
	2 &3	*No comparisons made, there were no differences found at this visit.*		

*significant difference found.

a. Hypothesis 1: Overall physical composite scores (PCS) of the SF-36 scale will be highest in psychiatry and primary care, and lowest in care coordination.

A pairwise comparison of the PCS scores per provider group was conducted using the Jonkheere-Terpstra trend statistic to determine trends over visits and between

groups. There was a difference found between groups at visit one, $T_{JT} = 2{,}595$, $z = 3.4$, $p = .001$, and at visit three $T_{JT} = 1{,}656$, $z = 2.5$, $p = .01$. There were no differences found at visit two $T_{JT} = 1{,}425.5$, $z = 1.662$, $p = .09$. and therefore no pairwise comparisons were completed (Table 21). This hypothesis was supported.

Table 22

Pairwise comparison QOL PCS

Visit	Pairwise comparison	Statistic
1	*CC < PC	$T_{JT} = 763$, z = 3.3, $p = .000$
	*CC < PS	$T_{JT} = 1{,}036$, z = 4, $p = .000$
	PS compared to PC	$T_{JT} = 1{,}155$, z = .522, $p = .30$
2	No differences noted	$T_{JT} = 1{,}425.5$, z = 1.662, $p = .09$
3	*CC < PC	$T_{JT} = 357$, z = 44.4, $p = .009$
	*CC < PS	$T_{JT} = 618$, z = 3.05, $p = .001$
	PS compared to PC	$T_{JT} = 618$, z = .412, $p = .32$

*indicates a difference
CC = Care coordination
PC = Primary care
PS = psychiatry

b. Hypothesis 2: When comparing by provider types, physical functioning scores in the SF-36 scale will be the highest in psychiatry and primary care and the lowest in care coordination.

Physical function scores were different between provider groups at visit one $T_{JT} = 2{,}743$, $z = 2.4$, $p = .02$, and visit three $T_{JT} = 1{,}580.5$, $z = 2.0$, $p = .045$, but not at visit 2, $T_{JT} = 1{,}419.5$, $z = 1.4$, $p = .150$. At visit one and visit three, care coordination had poorer physical functioning quality of life scores, indicating more difficulty with activities of daily living than primary care, and psychiatry groups (Table 21). The hypothesis is supported.

Table 23

Jonkheere-Terpstra trend statistic
Pairwise comparison of the QOL- physical function

Visit	Pairwise comparison	Statistic
	*CC < PC	$T_{JT} = 740.5$, z = 3.0, p = .004
	*CC < PS	$T_{JT} = 959$, $z = 3.2$, $p = .002$
1	PS = PC	$T_{JT} = 1{,}043.5$, z = -.329, $p = .629$
2	No differences	$T_{JT} = 1{,}419.5$, $z = 1.4$, $p = .150$
	*CC < PC	$T_{JT} = 595$, z = 2.7, $p = .01$
	*CC < PS	$T_{JT} = 356.5$, z = 2.36, $p = .027$
3	PS = PC	$T_{JT} = 629$, z = 89.23, $p = .567$

*indicates a difference
CC = Care coordination
PC = Primary care
PS = psychiatry

c. Hypothesis 3: When comparing by provider types Role Physical scores in the SF-36 scale will be highest in psychiatry, and primary care and lowest in care coordination.

There were differences found between provider types at visit three $T_{JT} = 1{,}617$, $z = 2.3$, $p = .023$, but not at visit one $T_{JT} = 2{,}647$, $z = 1.9$, $p = .055$, or visit two, $T_{JT} = 1{,}368.5$, $z = 1.05$, $p = .294$. Care coordination had poor role-physical scores compared to psychiatry at visit two. (Table 22) for statistical pairwise comparisons. The hypothesis was partially supported.

Table 24

Jonkheere-Terpstra trend statistic, pairwise comparison of the QOL- role physical

Visit	Pairwise comparison	Statistic
1	CC compared to PC	T JT = 293.5, z = .938, p = .522
	*CC < PS	$T_{JT} = 563$, $z = 2.4$, $p = .038$
	PS compared to PC	$T_{JT} = 760.5$, z = 1.31, $p = .286$
2	No pairwise comparison	$T_{JT} = 2{,}647$, $z = 1.9$, $p = .055$
3	No pairwise comparison	$T_{JT} = 1{,}368.5$, $z = 1.05$, $p = .294$

*indicates a difference
CC = Care coordination
PC = Primary care
PS = psychiatry

d. Hypothesis 4: When comparing by provider types Bodily pain scores in the SF-36 scale will be highest in psychiatry, and primary care and lowest in care coordination.

There were differences between provider types found at visit one T JT = 2,818.5, z = 2.8, p < .01 and visit three, T JT = 1,627.5, z = 2.4, p = .019. Pairwise comparisons were completed for these visits (Table 23). Care coordination patients had more severe pain than primary care and psychiatry. The hypothesis is supported.

Table 25

Jonkheere-Terpstra trend Statistic-Pairwise comparison of the QOL-Bodily Pain

Visit	Pairwise comparison	Statistic
1	*CC < PC	T JT = 694, z = 2.4, p = .024
	*CC < PS	$T_{JT} = 944.5, z = 3.0\ p = .004$
	PS compared to PC	$T_{JT} = 1{,}180, z = .717, p = .710$
2	No pairwise comparison	$T_{JT} = 2{,}647, z = 1.9, p = .055$
3	*CC < PS	$T_{JT} = 599, z = 2.78, p = .008$
	CC compared to PC	$T_{JT} = 333.5$, z = 1.84, p = .098
	PC compared to PS	$T_{JT} = 695$, z = .284, p = .851

*indicates a difference
CC = Care coordination
PC = Primary care
PS = psychiatry

e. Hypothesis 5: When comparing by provider types, General Health scores in the SF-36 scale will be highest in psychiatry and Primary care and lowest in care coordination.

There were no differences between provider type noted for any visit. Visit one results are $T_{JT} = 2{,}469$, $z = 1.03$, $p = .303$. Visit two results are $T_{JT} = 1{,}329.5$, $z = .748$, $p = .455$. Visit three results are $T_{JT} = 1{,}455.5$, $z = 1.075$, $p = .282$. This hypothesis is not supported.

4. Do patients with MDD or DDNOS who are participating in a pharmacogenetics testing study have differences in the mental components (vitality, social function, role emotion, and mental health) of the SF-36 scale by provider type?

Table 26

Estimated Marginal Means for Mental Composite Score

Provider type	*M*	*SE*	*df*	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Care Coordination	41.30	2.01	120.30	37.31	45.29
Primary Care	28.73	1.59	121.31	25.59	31.87
Psychiatric Care	33.33	1.35	111.14	30.65	36.01

Care coordination had better quality of life for their mental health than primary care or psychiatry patient's F (2,118) = 12.01, p <. 001. MCS was different at visit one T_{JT} = 1,542.5, z = -3.56, p < .001.

a. Hypothesis 1: When comparing by provider types, mental composite scores of the SF-36 scale will be highest in primary care and care coordination and lowest in psychiatry (Table 24).

Care coordination had better mental health quality of life scores than primary care T_{JT} = 152, z = -4.765, p <. .001, and psychiatry T_{JT} = 224, z = -4.7, p < .001. There were no differences between primary care and psychiatry, T_{JT} = 1,166.5, z = .610, p = .729. This hypothesis was not supported.

b. Hypothesis 2: When comparing by provider types, Vitality scores in the SF-36 scale will be the highest in primary care and care coordination and lowest in psychiatry.

There were no differences among provider types or visits for vitality scores. Therefore, there were no pairwise comparisons. At all visits vitality did not differ, visit one, T_{JT} = 1,999.5, z = -1.3, p = .19, visit two, T_{JT} = 1,071, z = -1.23, p = .22 and at visit three T_{JT} = 1,109, z = -1.49, p = .136. This hypothesis was not supported.

c. Hypothesis 3: When comparing by provider types, Social function scores in the SF-36 scale will be the highest in primary care and psychiatry and lowest in care coordination.

There were no differences among provider types or visits. Therefore, there were no pairwise comparisons. At all visits social function did not differ, visit one, T_{JT} = 2,130, z = -.67, p = .51, visit two, T_{JT} = 1,406.5, z = 1.35, p = .18 and at visit three T_{JT} = 1,432, z = .913, p = .361. This hypothesis was not supported.

d. Hypothesis 4: When comparing by provider types, Role Emotional scores in the SF-36 will be the highest in primary care and care coordination and lowest in psychiatry.

There were no differences among provider types or visits. Therefore, there were no pairwise comparisons. At all visits role emotional scores did not differ, visit one, T_{JT} = 2,010, z = -1.3, p = .21, visit two, T_{JT} = 1,397, z = 1.3, p = .21 and at visit three T_{JT} = 1,397, z = 1.3, p = .205. This hypothesis was not supported.

e. Hypothesis 5: When comparing by provider types, Mental Health scores will be the highest in primary care and care coordination and lowest in psychiatry.

There was a difference between providers at visit one, $T JT$ = 1,572.5, z = -3.43, p = .001. Care coordination had better mental quality of life than primary care $T JT$ = 236, z

= -3.67, $p < .001$, and psychiatry $T JT = 283$, z = -4.1, p < .001. However, there was no difference found between primary care and psychiatry $T_{JT} = 1{,}053.5$, $z = -.25$, $p = .4$. This hypothesis was not supported.

5. How does the study population's genetic phenotype (poor metabolizer, intermediate metabolizers, ultra-rapid metabolizer) in all provider types compare to the general population genetic phenotypical frequency rates?

Table 27

Comparison of Genetic phenotypes to Caucasian

	CYP 2D6 *%*	**CYP 2B6** *%*	**CYP 2C9** *%*	**CYP 2C19** *%*	**CYP 1A2** *%*	**CYP 3A4** *%*
PM	n = 13	n = 1	n = 1	n = 2	n = 2	n = 2
study %	10.7	0.8	0.8	1.7	1.7	1.7
Caucasian %	10		2 to 4	2 to 20		
EM	n = 49	n = 41	n = 66	n = 47	n = 109	n = 103
study %	40.5	33.9	54.5	38.8	90.1	85.1
Caucasian %	48		60	14 to 44		
IM	n = 30	n = 25	n = 16	n = 28	n = 2	n = 1
study %	24.8	20.7	13.2	23.1	1.7	0.8
Caucasian %	35		35	24 to 36		
IM^	n = 25	n = 43	n = 32	n = 2	n = 3	n = 10
study %	20.7	35.5	26.4	1.7	2.7	8.3
UR	n = 0	n = 0	n = 1	n = 37	n = 0	n = 0
study %	0	0	0.8	30.6	0	0
Caucasian %	0	0	0	30	0	0

PM (poor metabolizer), EM (extensive metabolizer), IM (intermediate metabolism), IM^ (Intermediate metabolism clinical indication), UR (ultra-rapid metabolism).

For allelic distributions refer to Appendix H (Tables 26 – 31). Genetic results of the sample, mimic the Caucasian population (Table 26).

Additional Analysis

As a secondary analysis, not included in the research questions, an evaluation of the "acknowledgment form" was conducted. This form was described in previous chapters and is listed in Appendix A. This form was given to all providers with the PGXr. Providers were instructed to return the form indicating a 'yes' or 'no' response to any medications changed because of the PGXr. In addition, they were asked if the patient acknowledged that the medication changes were based on the PGXr, and another 'yes' and 'no' response. This yes or no acknowledgement was added to the mixed linear model as a covariant for the study. Participants who had providers return the form were included in the analysis.

All participants with missing documents were excluded from this analysis, so the total sample for each group included 22 care coordination patients, 29 primary care patients, and 49 psychiatry patients. A summary of the breakdown of yes and no responses by provider group is below (Table 28).

Table 28

Providers indicating no or yes to acknowledgement form

	No	**percent**	**Yes**	**percent**
Care coordination	2	7.7	20	76.9
Primary care	10	24.4	19	46.3
Psychiatry	26	48.1	23	42.6

A comparison of patients who received responses for the acknowledgement form and those who did not had results as listed in the following tables (Table 29-32).

Table 29

Depression severity (PHQ9) interaction with acknowledgment by group

Parameter	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Care coordination with yes response	99.615	-4.399	.000*	-9.293293	-3.515749
Care coordination with no response]	97.820	-1.158	.250	-11.013160	2.898428
Primary care with no response	91.824	-.353	.725	-4.051406	2.827432
Primary care with yes response	93.473	.503	.616	-2.111065	3.544942
Psychiatry group with yes response	87.831	15.830	.000*	13.108840	16.872816
Psychiatry group with 'NO' response	88.643	-1.438	.154	-4.461598	.714919

*significant finding

Table 30

QIDS and acknowledgment

	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Care coordination "No' acknowledgement	-.54	2.65	192.82	-.20	.84	-5.78	4.69
Care coordination 'yes' acknowledgement	-1.97	.99	231.58	-1.97	.049*	-3.94	-.007
Primary Care 'No' acknowledgement	.11	1.29	227.69	.09	.93	-2.43	2.66
Primary care 'Yes' acknowledgment	.74	.99	237.43	.75	.46	-1.21	2.69
Psychiatry 'NO' acknowledgement	-.34	.90	243.94	-.38	.70	-2.12	1.43
Psychiatry 'Yes' acknowledgement	12.02	.65	245.62	18.3	.000*	10.72	13.30

**indicates significant result*

Table 31

Mental Composite Scores and acknowledgement

Parameter	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Care coordination ‘Yes” response	97.63	2.025	.046*	.29	28.64
Care coordination “no’ response	96.96	2.71	.008*	2.16	14.03
Primary care ‘no’ response	94.68	-.68	.49	-9.70	4.7
Primary care ‘yes’ response]	96.24	-1.50	.13	-10.57	1.45
Psychiatry ‘no’ response	95.06	-.17	.86	-5.94	4.97
Psychiatry ‘yes’ response	96.84	19.41	.000*	40.15	49.29

*indicates significant findings

Table 32

Physical composite score interaction with acknowledgment

Parameter	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Care coordination 'no' response	94.614	-.904	.369	-23.417909	8.768762
Care coordination 'yes' response	96.993	-2.744	.007*	-16.191572	-2.599955
Primary care 'no' response	97.516	1.042	.300	-3.947478	12.678172
Primary care 'yes' response	98.018	1.132	.260	-2.970266	10.858393
Psychiatry 'no' response	96.534	.465	.643	-4.801860	7.738867
Psychiatry 'yes' response	96.844	19.421	.000*	40.146671	49.286616

When the statistical model was conducted, some interesting interactions were found regarding the change in depression severity scores. Both the care coordination group (*b = -6.40, t = -4.399, p <.0001)* and the psychiatry groups (*b = 14.99, t = 15.83, p <.0001)* who had 'yes' responses to the acknowledgment of medication change had interaction for changes in depression severity of provider type, and acknowledgment. Primary care patients had no interaction. Also, these two groups had interactions of physical and mental composite scores (Table 30 and 31). This model takes into consideration change over visits for depression severity, study provider, and acknowledgment status.

This chapter has presented the results of this study, and a discussion of the major findings will follow in chapter 5. This study was conducted to evaluate by provider type including care coordination, primary care and psychiatry, the change of depression (PHQ-9), depressive symptoms (QIDS-SR16) and quality of life (SF36) over time in a

population of patients diagnosed with MDD or DDNOS while participating in a study for pharmacogenetics testing. This chapter presented the quantitative results using mixed linear models, Jonkheere-Terpstra trend statistics, one-way ANOVA, frequencies, and used descriptive statistics to answer the research questions presented in chapter 3.

CHAPTER 5
Discussion

This Chapter discusses the results of the findings. Strengths and limitations of the combined data set are discussed. Additionally, clinical implications will be considered with recommendations for future research. The study was conducted to evaluate by provider type including care coordination, primary care and psychiatry, the change of depression (PHQ-9), depressive symptoms (QIDS-SR16) and quality of life (SF36) over time in a population of patients diagnosed with MDD or DDNOS while participating in a study for pharmacogenetics testing

Participant Demographics

There was no difference between the three groups regarding age or gender proportions. However, this study had slightly more females than males and more females than other studies of depression. An evaluation of insurance type showed that most of primary care and psychiatry had private insurance, while care coordination participants mostly had Medicaid, which was indicative of the population.

Most of the participants were married or single, but care coordination, had a higher percentage of divorced patients and most resembled other studies of depression. Primary care had the lowest percentage of participants who were employed, and psychiatry patients had the highest percentage who were employed. Care coordination had the highest percentage of disabled participants, and psychiatry had the highest percentage of retired participants. Care coordination is a program that is offered to patients who are Medicaid or Medicare, who meet specific criteria for physical and mental illness, so this difference is not unexpected.

Care coordination had twice as many chronic health conditions and twice the number of medications than both primary care and psychiatry groups. It is possible that care coordination participants had a decreased emphasis on mental health because of physical health complications. More medication use can also complicate prescribing for depression and affect medication pharmacokinetics and thus effectiveness.

Primary care and psychiatry studies controlled for mental health conditions. Care coordination did not control for other mental health conditions, allowing for mental health comorbidities. Interestingly, there was no difference between groups concerning number of mental health conditions.

Discussion of Research Questions

Overall group changes. All patients together, regardless of group, showed a decrease in depression severity, depression symptoms and an increase of mental composite quality of life from visit one to visit three. Participants baseline scores started at high moderate and decreased to the low moderate level at visit three for depression severity. The decrease in symptoms indicated a change from moderate symptoms at baseline to minimal at the third visit. This decrease in depression severity and symptoms also resulted in an improvement in mental quality of life. But, quality of life reveals no change in physical composite scores. Overall, patients who were receiving treatment through the study improved for all measures, excluding physical composite scores. Primary care and psychiatry groups had higher numbers of participants which may have influenced these total sample results. Care coordination had the fewest number of participants and therefore the smallest impact on overall changes for the group as a whole.

Depression severity (PHQ9).

The objective for this study was to evaluate differences in depression severity between groups. Results indicate that care coordination was less depressed and had lower depression severity, than primary care and psychiatry patients. Level of depression was similar between primary care and psychiatry patients. Additional analysis assessed change over time in each provider group. Because participants in care coordination are complex patients, there was a question about the inability of patients to decrease depression severity during the three time points, and this proved true. Care coordination did not improve their depression severity over time. However, care coordination participants had low moderate levels of depression to begin the study, and improvements from that level of depression may take more time and higher sample size to see statistical improvements. On the other hand, this may be representative of fluctuations within a chronic underlying depression that is comorbid with chronic illness.

Primary care and care coordination participants had decreases in their depression severity from baseline to time three. About fifty percent of participants in both groups were able to reduce their depression from baseline levels of moderate to severe depression to mild depression category. This is a clinically important point for this study, suggesting that primary care providers are as effective as psychiatrists in managing depression severity.

The conclusions for depression severity in this study are consistent with previous studies, such that primary care and psychiatry patients tended to have similar depression severities. Primary care and psychiatry levels were in the severe depression range. There were decreases in both primary care and psychiatry in depression severity scores over the

course of three visits, but no change in care coordination. Mostly likely, this lack of change is a reflection of the lower baseline scores in the care coordination group, and that there were no inclusion criteria to control for higher depression rates.

Depression symptoms (QIDS).

There was no interaction between provider type, change over time and depression symptoms. However, it is interesting that compared to an analysis of combined participants which indicated improvements in symptoms, the individual provider groups did not all show decreases. Care coordination participants did not have decreases in symptoms, which was probably attributed to health problems which potentially interfered with the patient's ability to separate depression related symptoms from illness related symptoms.

Both primary care and psychiatry participants had decreases in their depression symptoms. This finding suggests that those who see primary care providers, but are not part of the care coordination program are able to discern differences in depression symptoms compared to chronic illnesses. While not measured, another possible factor is that they had higher health literacy. Participants mean symptoms at baseline were higher in primary care than psychiatry patients, but not significantly so. This finding may lend validation to previous studies which indicate more somatic complaints noted in primary care than psychiatric patients. Mean symptoms were also consistent with previous studies conducted.

Quality of Life (SF36)

Physical Composite Score. The SF-36 instrument assesses physical quality of life and mental quality of life as two main scores. Low scores on the quality of life scale

indicate poor quality of life while high scores indicate better quality of life. The care coordination group had poor physical quality of life, in 'physical composite scores', 'physical function' scores, 'role physical' scores, and 'bodily pain' scores, compared to the primary care and psychiatry groups. Having low scores at most of the visits for care coordination patients indicates poor daily physical function. Patients in care coordination tend to have more chronic conditions, some of which are pain related. Previous literature as discussed in chapter three, indicates that depression contributes to increasing disability with activities of daily living when a physical impairment also exists. Previous studies have reported that primary care patients had more impaired quality of life over psychiatry patients. Our sample shows that primary care and psychiatry patients are similar in physical function with little problems in completing tasks of daily physical life.

Interestingly, there were no differences in patient's self-evaluation of 'general health' among provider types. General health measures on the quality of life indicate one's outlook on their future health. This indicates that all patients had a similar outlook on their future health.

Care coordination patients had higher 'mental composite score's than primary care and psychiatry patients. This was an unexpected finding as the components of the 'mental composite score' include the four subscales of 'vitality', 'social function', 'role emotion' and 'mental health'. The only subscale differences noted for mental composite scores between provider types were the overall 'mental composite score' and 'mental health score.' Primary care and psychiatry groups had lower 'mental composite scores' indicating higher levels of stress and depression-related social disabilities than the care coordination group. Also, primary care and psychiatry patients had poor 'mental health

scores', which indicates a more persistent and sustained depression. In these two areas, care coordination patients had a better quality of mental health than either primary care or psychiatry patients. Again, this may be related to primary care and psychiatry groups having higher PHQ9 scores at study entry, which signifies higher levels of depression. Primary care patients and psychiatry patients tended to have poor quality of life, and high levels of depression. This combination of depression and quality of life is similar to previous studies.

This study found that the care coordination group differed from both primary care and psychiatry groups for depression severity PHQ9, and SF36. Interestingly, care coordination patients had less severe depression and high quality of life scores, indicating a good quality of life. Studies of depression that also evaluated the quality of life reported that those with more severe levels of depression had a poor self-reported quality of life measurement. The fact that quality of life scores were higher in care coordination patients, could be explained by the differing inclusion criteria. The care coordination group did not have a baseline depression score restriction of ≥ 10 while primary care and care coordination did have this limitation.

Pharmacogenetic phenotypes. Pharmacogenetics testing was completed on most of the participants, with a pharmacogenetic guidance report (PGXr) conducted by genetic pharmacists for the study sample. The genetic data was collected for the three individual studies but were combined for this study. This study reported the frequency of phenotypes as they relate to the general population.

All three studies had a pharmacogenetics component, and this question was simply to describe our study sample. Reported genetic phenotypes were very similar to a

general Caucasian population, which means that this study may be generalized to a larger population of Caucasians. There was initially speculation that because patients in care coordination had such complex medical conditions paired with large numbers of medications, that perhaps this study sample may have a higher incidence of genetics related to poor enzyme function in the liver to metabolize medications appropriately. However, results were similar to reported population averages.

Acknowledgement forms

Response to the acknowledgment forms was highest for care coordination and lowest for primary care. Both the care coordination and psychiatry groups had improvements in depression severity and symptoms in those patients who the provider returned the acknowledgment form with a "yes" as opposed to a "no" response. Interestingly, care coordination did not have a significant decrease of depression related symptoms overall. This may be for several reason including the possibility that provider engagement, or medication changes based on pharmacogenetics was a mediator to change.

When PCS and MCS for the quality of life measures were evaluated, care coordination patients showed an interaction of provider type and PGXr acknowledgement either way, 'yes' or 'no', for MCS. Both yes and no acknowledgement were significant. This finding may be because there was a small sample size and small change in MCS or related to contact with care coordination. The psychiatry group had an interaction as well, but only for those who answered 'yes' to the acknowledgement. Primary care showed no interactions.

In addition, care coordination and psychiatry groups also had significant changes for PCS for those whose provider returned the form with a "yes". Primary care again had no change. It is easy to suspect that there were changes in physical quality of life in the care coordination patients because this sample of patients scored very low in this category, and any improvement could be noteworthy. In addition, if medications were made based on the PGXr with the patient's acknowledgment the patient could have a sense of improvement. It is unclear, however, this author speculates that patients were more engaged by the research team and residents regarding changes that occurred in psychiatry.

The PGXr acknowledgement form and process results need more clarification and study. It is unclear if the form is a good indication of patient understanding and acknowledgment to medication changes based on pharmacogenetics because it was a provider form. Patients did not fill out the form and return. A more controlled study, with a questionnaire related to patient acknowledgement of and understanding of changes made because of pharmacogenetics would have better validity. However, the finding suggest that care coordination was more aware of the processes, and changes based on this study's findings. This conclusion, however, must be viewed with caution based on these results. Evaluation of patient's awareness of the pharmacogenetics processcertainly needs future more controlled study.

Nursing Theory relationship

Dorothea Orem's SCDT explains factors that specifically relate to the care coordination participants. For example, three perspectives contribute to self-care, conditioning factors, psychophysiological factors of health and disease and behavioral

resources and demands. The care coordination participants had a combination of physical and mental health needs, and many were lacking resources. Some care coordination participants were homeless, lacked financial resources and had limited health literacy. Nursing guidance is important when patients have low health literacy to help guide patients in, for example, behavioral changes and understanding medications. The lack of health literacy, lack of financial resources and physical complication to basic everyday activities, can cause deficits in self-care abilities and these are evident in the low physical composite scores noted in the care coordination group compared to the primary care and psychiatry group. These deficits may be filled by nursing resources and programs such as care coordination and care transitions programs.

The deficits noted in the quality of life for the physical component in care coordination reflect lack of self-care agency. Self-care agency is the power and ability to care for oneself. Patients in the care coordination group had worse physical scores in 'role-physical' and 'physical function' on the quality of life measure. 'Role physical' indicates deficiencies at work or with employment due to the interference of physical problems. In addition, 'physical function' is a limitation of daily activities of living. The care coordination group had the highest percentage of physically disabled and unemployed participants, which is evidenced in the physical quality of life total score and sub-scale scores. These indicators of quality of life reflect a need for nursing intervention.

Strengths of the study.

This study had several strengths such as similarities in study design between the three samples, use of the same questionnaires and similarities of visit timelines. Having

care coordination as a group comparison added more information to previously published literature and filled the literature gap. The willingness of providers and nursing staff to assist with this study also was a strength for data collection and the reduction of patients becoming lost-to-follow-up.

This study added a unique picture of depression in three unique samples. Evaluation of primary care and psychiatry patient's depression has been previously researched. The addition of care coordination with this the population's physical limitations, low health literacy, high health care utilization and health complexities added an interesting perspective to the comparison.

Challenges and Limitations

There were multiple challenges and limitations beginning with enrollment. When the three studies were designed, it was predicted that the care coordination study would complete enrollment quickly. However, protocol inclusion criteria which restricted insurance type limited the sample size; therefore, an amendment was completed. While recruitment increased, the process was slow and numbers remained low for care coordination. The primary care group had no research coordinator at the clinics to guide the research process, so enrollment and follow-up visits were completed over the phone and through the mail. This process increased the number of missed or delayed visits. The psychiatry group had the highest enrollment number as the study was overseen by medical residents and research staff Psychiatry also had the fewest missed visits and patients lost to follow-up. At the time the analysis was completed, participants were at various stages of the study and contributed to missed visits and incomplete data

collection. Missing data can be a significant problem associated with increasing bias, and creating issues with sample size.

Self-report measures are also a limitation in survey research because the researcher must rely on a patient's ability to be introspective and truthful about one's condition. Some problems may occur because participants were unwilling to answer certain questions or avoided truthful responses. Additionally, the patient answered the same questionnaires multiple times, which may have caused the patient to anticipate questions and report on them differently. Furthermore, the choice of participating clinics for all provider types, care coordination, primary care, and psychiatry was limited to a convenience sample of within-health system participation. The lack of randomization can lead to biased results..

Additionally, the purpose of the care coordination study was not originally to make a comparison between groups, and so the depression severity inclusion criteria were slightly different than the primary care and psychiatry studies. This had a potential influence on the outcomes noted for care coordination. Along with this difference, the care coordination participants had restrictions on the type of insurance that the patient could have to enter the study.

Future Implications. Future study recommendations include the addition of the patient activation measure (PAM), to fully understand how engaged the care coordination patient is compared to primary care or psychiatry. Using a measure of patient activation may offer data and insight on components associated with self-care activities.

This study evaluated overall numbers of symptoms using the QIDS self-report form. However, an evaluation of the types of symptoms experienced overall and between

each group may shed more light on the care coordination group's differences. Additionally, an understanding of depression symptoms and which specific symptoms were reduced may be important to understand the overall effect and impact on patients. Other studies found that most people experienced sexual side effects when on antidepressant medication. This analysis was not completed with this study but will be conducted later.

Cost outcomes are an important measure of clinical use. Does pharmacogenetics testing improve future cost expenses to patients and health systems? This has yet to be addressed. The centers for Medicare and Medicaid, are reimbursing some pharmacogenetics testing such as for clopidogrel, an antiplatelet medication, which has been shown to have clinical utility and decreases costly health and economic outcomes for both patients and hospital systems. However, reimbursements are few and far between for other indications such as in mental health applications.

Nursing influence on outcome was not the primary goal of this study; however, this study contributes to baseline understanding of depression in the care coordination sample compared to primary care and specialty care settings. Future studies are needed to understand nursing's influence for improving outcomes for patients with depression through participating in care management or care coordination. This study shows that the care coordination participants are a unique study sample with individualized needs which can be met with patient centered-care coordination. This study speaks directly the care coordination competencies and nursing's ability to provide care for those in self-care deficit.

Summary

This study evaluated differences in depression severity (PHQ9), depression symptoms (QIDS), and quality of life (SF36) in three populations of patients being treated by different providers. The three providers included care coordination, primary care and psychiatry. The study compared patients from three provider groups who all had major depression disorder, or depression diagnosis-not otherwise specified. All three studies used the same questionnaires at the same intervals, PHQ9, QIDS, and the SF36.

Care coordination was different from primary care and psychiatry on many levels. There were no inclusion criteria to control for baseline depression severity levels and mental composite quality of health which revealed that care coordination participants have lower depression severity compared to the other groups. This finding suggesting that care coordination's depression is not as severe as primary care or psychiatry patients should be taken with caution since primary care and psychiatry inclusion criteria dictated higher levels of depression for all participants. Care coordination group's mental quality of health is also much better than the other groups. Care coordination group had more chronic illness and may be related to secondary depression caused by chronic illness. It was clear that care coordination participants had more chronic conditions and more complex situations because they also had the highest number of chronic diagnoses and highest number of medications compared to primary care and psychiatry patients. Overall, the chronic conditions found in care coordination appear to contribute to the mild to moderate depression found in this population.

Care coordination was had less depression severity and less symptoms but better mental quality of life than primary care and psychiatry patients. In addition, care

coordination had more chronic conditions and polypharmacy use, which was reflected in their poor quality of physical health scores. However, there were parallels found between primary care and psychiatry patients. Primary care and psychiatry patients had similar depression severity, similar depression symptoms and similar quality of life scores for both physical and mental composite scores. Depression in the primary care population has been studied as previously discussed in the literature review, and it has been identified as having more somatic symptoms than patients in psychiatry. This finding was not supported in this study, however, given a larger sample size, perhaps this would have been the case. Overall, the similarities between primary care and psychiatry patients was consistent with previous studies.

Conclusion

This study illustrates differences in care models which have the potential to influence patient depression outcomes and that primary care and psychiatry patients follow similar trends and characteristics. Pharmacogenetic care may influence patient's engagement, decrease depression severity and symptoms and improve quality of life. Care coordination patients differ from primary care and psychiatry patients in depression severity, depression symptoms and physical quality of life. At its most elemental, this study has shown that care coordination participants have unique challenges and some advantages over primary care and psychiatry patients. Care coordination participants have multiple challenges, because they have complex chronic illness in combination with mental health issues preventing or hindering activities of daily living. The strengths of care coordination are the nursing leaders along with social workers who guide

participants care, strengthen the process of transitions, and navigation of the complex system of healthcare we have today

Additional strengths for the care coordination group are that they had less depression and higher quality of life. Previous studies directed attention toward managed care which might increase follow-through for patients and potentially better outcomes. Nursing is situated to make a large impact on the possible outcomes for depressed persons through care coordination. Additional nursing interventions in all three settings would impact depression care and patient outcomes.

Appendix A
Acknowledgment form

PGX-TIME STUDY

Psychotropic Genotyping panel research study

Physician RESPONSE TO GENOTYPING PANEL report

Patient Name_____ DOB:_____

Physician Response Plan as a result of the Psychotropic Genotyping Panel for research study.

_____No medication changes planned

_____Change in medication:

Current Medication:_____

New Medication:_____

_____Change in Medication DOSAGE:

Current Medication/DOSE_____

New dosage:_____

Patient acknowledges medication change plans based on pharmacogenetic testing:

_____Yes

_____No

Date:_____

Physician Referring Patient to Study:_____

Staff completing form:_____

Phone:_____ Email_____

Appendix B

Pharmacogenetic resources

Resources for Clinical Guidelines in Pharmacogenetics	Information available
www.pharmgkb.org	CPIC guidelines, DPGW
http://medicine.iupui.edu/clinpharm/ddis/main-table/	CYP 450 pathways
https://pharmacogenomics.ucsd.edu/	pharmacogenomics education
http://www.nhlbi.nih.gov/research/resources/genetics-genomics/pgrn	Pharmacogenomics at NIH

Appendix C

Pharmacogenetic CYP substrate pathways of Antipyschotics

1A2	2B6	2C9	2C19	2D6	3A4,5,7
amitriptyline (Elavil®)	paroxetine (Paxil®)	amitriptyline (Elavil®)	amitriptyline (Elavil®)	fluvoxamine (Luvox®)	alprazolam (Xanax®)
fluvoxamine (Luvox®)		fluoxetine (Prozac®)	escitalopram (Lexapro®)	amitriptyline (Elavil®)	diazepam (Valium®)
asenapine (Saphris®)			Citalopram (Celexa®)	clomipramine (Anafranil®)	midazolam (Versed®)
olanzapine (Zyprexa®)				Desipramine (Norpramin)	triazolam (Halcion®)
clozapine (Clozaril®)			**CYP 2D6 (cont)**	doxepin (Silenor®)	**(SSRI)**
pimozide (Orap®)			haloperidol (Haldol®)	trimipramine (Surmontil)	vortioxetine (Brintellix)
Thiothixene (Navane®)			perphenazine (Prolixin®)	amoxapine (Ascendin®)	vilazodone (Biibryd®)
trifluoperazine (Stelazine®)			risperidone (Risperdal®)	imipramine (Tofranil®)	escitalopram (Lexapro®)
			thioridazine (Mellaril®)	fluoxetine (Prozac®)	Citalopram (Celexa®)
			zuclopenthixol (Clopixol®)	nortriptyline (Pamelor®)	lurasidone (Latuda®)
			iloperidone (Fanapt®)	protriptyline (Vivactil®)	aripiprazole (Abilify®)
			aripiprazole (Abilify®)	paroxetine (Paxil®)	
			quetiapine (Seroquel®)		
			chlorpromazine (Thorazine®)		

Bohlen, Mattheissenn, Weisser, 2014. Avera Institute for Human Genetics psychotropic panel, unpublished

APPENDIX D
Institutional Review Board Documents

March 30, 2015

Julie Kittelsrud, CNP Avera
Research Institute 2020 S. Norton
Avenue Sioux Falls SD 57015

Dear Ms. Kittelsrud:

Regarding Our Study # 2014.079
Protocol Title: Evaluation ofPharmacogenetic (PGX Testing in a Mental health population and Economic Outcomes (PGX-Time)

This is to inform you that the Avera IRB has reviewed your request regarding the above referenced research study. This is to confirm that I have approved your request.

Our Internal Number: 7770
The following items were reviewed

- **Protocol Amendment 2, dated 24-Mar-2015**
- **Patient Schedule of Participation, Amendment 2, dated 25-Mar-2015**
- **MMAS-8 Coding Questionnaire**
- **PAM-MH Questionnaire**

The study is subject to continuing review on or before **1/21/2016**. You are reminded that you are required to report any serious reactions to the Avera Institutional Review Board within ten (10) business days of it occurrence (or your knowledge thereof).

Please note that changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full Committee review. Contact the Avera Institutional Review Board, at (605) 322-4755, if you have any questions or require further information regarding this IRB Action.

Respectfully yours,

Sandra Ellenbolt

APPENDIX D

Matthew Stanley, D.O.
AMG University Psychiatry associates 4400 W. 69th Street
Sioux Falls SD 57108

RE: Our Study #2014.081

Dear Dr. Stanley:

Meeting Date: 12/17/2015
Protocol Title: Pharmacogenetic testing in an outpatient population of patients with Major Depressive Disorder or Depressive Disorder not otherwise specified with Avera University Psychiatry Associates.

This is to inform you the Avera IRB renewed its approval of the above research study. The renewal is granted for an additional **12 months.**

The Effective date of the renewal is **12/17/2015:** The approval period will expire on **12/16/2016**
The following items were reviewed:

- Continuing Review Report dated 3-Dec-2015
- Informed Consent dated 23-Jan-2015

All conditions for continued approval during the prior approval period remain in effect. These include, but are not necessarily limited to the following requirements:

- A stamped copy of the most current **Informed Consent Document** (as noted above) is included. No other consent documents should be used. Each subject must sign the approved ICD prior to initiation of any protocol procedures. The original signed informed consent document must be placed in each subject's medical/research chart. In addition, each subject must be given a copy of the signed consent document.
- All protocol amendments and changes to approved research must be submitted to the IRB and not be implemented until approved by the IRB except where necessary to eliminate apparent immediate hazards to the study subjects.
- Significant changes to the study site and significant deviations from the research protocol must be reported.

Please contact the Avera Dept of Human Subjects Protection (DHSP) at (605) 322-4706 if you have any questions about the terms of this approval.

Sincerely yours,

Sandra Ellenbolt

Sandra G. Ellenbolt, CIM, JD
Director, Department of Human Subjects Protection/IRB Chair

APPENDIX D

AMG University Psychiatry associates
4400 W. 69th Street Sioux Falls SD
57108

Dear Dr. Stanley:

Regarding Our Study # 2014.081

Protocol Title: Pharmacogenetic testing in an outpatient population of patients with Major Depressive Disorder or Depressive Disorder not otherwise specified with Avera University Psychiatry Associates

This is to inform you that on behalf of the Avera IRB I have reviewed your request regarding the above referenced research study. This request qualified for expedited review under FDA and NIH (OHRP) regulations. This is to confirm that on behalf of the Avera IRB I have approved your request.

Our Internal Number: 7678
The following items were reviewed and approved:

- **UPA Protocol Amendment 1 1.23.15**
- **UPA PGx Patient invitation letter Amend 1, 1.23.15**
- **UPA PGx Schedule of Participation Amend, 1.23.15**
- **UPA Patient Packet letter Amend 1, 1.23.15**
- **UPA Questionnaire packet letter Amend 1, 1.23.15**
- **FIBSER questionnaire**
- **Beck Depression Inventory II**
- **Telephone consent Script**

The requested changes to the protocol have been approved.

The study is subject to continuing review on or before **1/21/2016**. You are reminded that you are required to report any serious adverse events to the Avera Institutional Review Board within ten (10) business days of its occurrence (or your knowledge thereof).

Please note that changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full Board review. Contact the Avera Institutional Review Board, at (605) 322-4755, if you have any questions or require further information regarding this IRB action.

Respectfully yours,

Sandra Ellenbolt

APPENDIX E
Supporting documents for Informed Consent
AVERA HEALTH PLAN- PGX TIME
PSYCHOTROPIC GENOTYPING PANEL RESEARCH STUDY
SCHEDULE OF PARTICIPATION

	Screening Stabilization	Visit 1	visit 1A (letter/phone contact)	Visit 2	Visit 3	Visit 4	Visit 5
	3 months or longer	Day 0	Month 1	Month 2	Month 3	Month 6	Month 12
Procedure							
Enter Care Coordination	x						
Informed consent for the PGX study	x*[1]	x*[1]	x*[1]	x*[1]	x*[1]	x*[1]	x*[1]
Current medications	x	x	x	x	x	x	x
Medical history	x						
Demographics	x						
Adverse Events		x		x	x	x	x
Questionnaires		x		x	x	x	x
Pharmacogenetic testing							
PGx testing (blood drawn and sent to AIHG)		x					
PGX recommended changes begin			x				

*1. Informed consent may be completed on or before day 0, and is an ongoing process throughout the study.
*4. Short-Form-12, Quality of Life measurement
*5 STARD-Patient rated Inventory of Side Effects.

APPENDIX E

The Patient Health Questionnaire-9 (PHQ-9) is 9 questions and will ask you about your depression. It is used to help your care providers understand the severity of your depression.

The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) is a 16 item questionnaire which assesses for symptoms related to common symptoms experienced in depression.

The Short Form-36 (SF-36) health outcomes measure is 36 questions in length and addresses physical, social and emotional aspects about your health.

The STAR*D-Patient rated Inventory of Side Effects (STAR*D-PRISE) is 20 questions and will ask you about any side effects that may be related to taking antidepressant medications.

Frequency, Intensity and Burden of Side Effects (FIBSER) scale asks 3 questions about the frequency, intensity and burden of your side effects.

The following two Questionnaires will be taken by 100 participants at two time points (Day 0) and Month 3:

- **Patient Activation Measure-Mental Health (PAM-MH)** is a 13 item questionnaire which asks you about your confidence level and knowledge about your health care.

APPENDIX E

Supporting documents for Informed Consent

Avera Institute for Human Genetics

Protecting Your Rights and Privacy as a Research Participant

Your privacy is very important to us. Like any other clinic or hospital visit, we are required to keep your personal and medical information confidential before, during, and after your visit.

Our dedication to privacy extends beyond our doctors and nurses to include everyone employed in our healthcare family. We want you to feel safe knowing your personal and medical information is protected throughout Avera McKennan's entire healthcare system.

How will my personal information be protected?

Information collected for research studies is confidential. Data collected and the specimen bank are the property of the Avera Institute for Human Genetics. In the event of any publication regarding this study, your identity will not be disclosed.

Employees of the Avera Institute for Human Genetics and the Avera Institutional Review Board (IRB) may see parts of your medical records related to your participation in a study. The Avera IRB is a group of scientific and non-scientific individuals that helps protect the safety and welfare of subjects in research studies.

We will make every effort to protect your privacy. Here are just a few of the steps we will take:

- We will keep your data coded and secure to ensure that your sample(s) and information remain anonymous and can be used for quality research.
- We will remove your name and other identifiers from your sample(s) and information, and replace them with a code number. We will keep the list that links the code number to your name separate from your sample(s) and information. Only a few of the researchers will have access to the list and they sign an agreement to keep your identity a secret.
- Avera safety monitors or committees, as well as the Avera IRB, may have access to your records, but only in their role of ensuring the study is being done safely and correctly.

- Researchers who study your sample(s) and information will not know who you are. Disciplinary actions, including termination of employment, may result if an employee tries to determine your identity.
- We will not give information that identifies you to anyone, except if required by law. Information that is shared outside of the Avera Institute for Human Genetics may no longer be protected by the federal privacy law called "HIPAA"; however, it will be protected as described in this form and may be covered by other privacy laws.
- The results of a study could be presented at a scientific meeting or published in an article, but would be presented as a general analysis of many study donations and would not include any information that would let others know who you are or any other study participants are.

Who can see or use my information?

Signing a study's informed consent document gives the researchers your permission to obtain, use, and share information about you for the study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care.

Information about you may include information about your health and your medical care before, during, and after the study, even if that information wasn't collected as part of the research study. For example:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records
- Alcohol/substance abuse treatment records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during the study. Examples include the following:

- The researchers may need the information to check your test results or look for side effects.
- Avera Institute for Human Genetics and government officials may need the information to make sure that the study is done properly.
- Organizations that are funding the study may need the information to make sure that the study is done properly.
- The researchers may need to use the information to create a data bank of information about your condition or its treatment.

What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until is destroyed, Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include the following:

- To avoid losing study results that have already included your information.
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help the Avera Institute for Human Genetics and government officials make sure that the study was conducted properly.

If you have questions about your rights in the study, you should contact:

Avera Institutional Review Board

3900 West Avera Drive

Sioux Falls, SD 57108

(605) 322-4755

Informed Consent for Psychotropic Genotyping Panel Research Study

First name: _____ Last name: _____

DOB: _____ ❑ Male ❑ Female

Test to be completed: ____Psychotropic Genotyping Panel_____

Purpose of the Study

You are invited to volunteer to be in a research study to evaluate the effectiveness of determining the right medications based on your genetic profile. This genetics testing uses a blood sample to get a snap shot of how your liver will metabolize medications; it will not show risk for getting a disease. The primary objective of this study is to draw blood and find out which medications, based on your individual genetics, might work best in treating you. This type of testing is currently available as a service at Avera and other laboratories; however, we hope that this study will support and/or add to the use of this genetic testing in clinical practice.

You have been identified by your physician as meeting criteria for this research study. This blood test is not a treatment; the genetic analysis, along with other information, will be considered by professionals to make clinical medication recommendations for your treatment. With your consent, your medical history, demographics, and list of medications will be accessed and utilized by research staff to make these recommendations to the providers involved in your care. This study will use questionnaires to measure the effectiveness in providing this genetic testing.

Study Involvement

If you consent to take part in this study, your physical involvement is limited to about 12 months and will include informed consent, collection of a blood sample, standard care clinic visits, and questionnaires taken about every 3 months over that time. You will need to visit an Avera Laboratory draw location to have your blood drawn. Lab staff will collect two purple-top EDTA tubes, with at least 2 ml (about ½ a teaspoon) in each tube. It may also be necessary for research staff to contact you regarding questionnaires or for other information needed for the conduct of the study. Your consent will also allow staff to access your medical records for the 12 months prior to your enrollment into this research study. Please refer to the Psychotropic Genotyping Panel Research Study Schedule of Participation for a more detailed explanation of procedures and questionnaires. Also, with your consent, your blood sample will be stored in the Avera Institute for Human Genetics (AIHG) Specimen Bank indefinitely for use in studying future genetic and genomic issues. Your sample will be coded in order to protect your identity in any future studies.

Privacy and Confidentiality

Your privacy is very important to us. We are required to keep your personal and medical information confidential before, during, and after your clinic visit. At all times, Avera has appropriate administrative, technical, and physical safeguards in place to protect the privacy of

your personal health information. Your genetic report will be entered into your Avera electronic medical record and will only be accessed by clinicians directly involved in your care and by designated research staff involved in this study. Your genetic report is confidential to the extent required by law and may only be released to other medical professionals with your written consent. We want you to feel safe knowing our personal and medical information is protected throughout Avera's entire healthcare system. Our dedication to privacy extends beyond our doctors and nurses to include everyone employed in our healthcare family.

Benefits and Risks of Participation

This pharmacogenetic test only looks at how your body processes (or metabolizes) medications, providing clinicians with a tool for prescribing the safest and most effective medications, helping avoid adverse effects. Your doctor will receive a report that tells which medications may help best treat you. If you have "normal" metabolism, your doctor will prescribe medications based on current best practice standards, the same as if you do not have this test.

Although the chance is small, there is a risk that someone could get access to the data confidentially stored about you. There is also the risk someone could trace the information in a scientific database back to you. Even without your name or other identifiers, genetic information is unique to you. The Genetic Information Nondiscrimination Act (GINA) generally protects you against discrimination based on your genetic information when it comes to health insurance and employment. Please refer to the AIHG Protecting Your Rights and Privacy as a Research Participant document for additional information on how your personal and medical information is protected.

Discomforts associated with the blood draw may include brief pain, slight bleeding, or a bruise from the site. Rarely, a small blood clot or infection could originate from the site of the needle puncture. In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you. If you have an illness or injury during this research study that is not directly related to your participation, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

There is no compensation for taking part in this research study. This study will pay for the cost of the blood draw and genetic testing. Any required study-related visits outside of standard of care for your treatment may be covered under this research. Ask the study staff if you have any questions about bills, fees or other costs related to this study.

Voluntary Participation and Withdrawing Participation

Your participation in this study is voluntary. You may refuse to participate, or may stop participation at any time, even after signing this document, without a penalty or loss of benefits to which you are otherwise entitled now and in the future. Your participation may also be stopped by the study physician without your consent, if he/she feels that is best for you. If you choose to stop your participation, the researchers will destroy any remaining blood sample and will stop using or disclosing information about you. Sometimes, however, it may be necessary for information about

you to continue to be used or disclosed, even after you have canceled your permission or the study has ended. An example of this would be to show auditing authorities that the study was conducted properly.

Volunteer's Statement

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Do not sign this consent form unless you have had a chance to ask questions, and have received satisfactory answers to all of your questions. If you have additional questions about taking part in this study, would like to withdraw, or have a research-related injury, you may contact the Avera Institute for Human Genetics at (605) 322-3050. If you have questions about your rights as a research participant, call the Avera Department of Human Subjects Protection at (605) 322-4706.

□ Yes, I want to donate any remaining blood sample to the AIHG Specimen Bank. Checking this box provides my consent to have my stored blood sample to be used for future research, as well as for access to my Avera electronic medical record, if needed. I understand I may withdraw this consent at any time by calling AIHG at (605) 322-3050.

□ No, I *do not* want to donate any remaining blood sample to the AIHG Specimen Bank.

I have read and understand the above information. I understand taking part in this research study is voluntary. I understand I may quit the study at any time without harming future medical care or losing any benefits to which you might otherwise be entitled. I have received the AIHG Protecting Your Rights and Privacy as a Research Participant and Pharmacogenetic Research Schedule of Participation documents. I will be given a copy of this signed document by requesting a copy by calling the phone number listed below. By signing below, I am agreeing to take part in this study.

_____	_____	_____
Name of Patient (Print)	Signature	Date (day, month, year)

_____	_____	_____
Name of Person Obtaining Consent (Print)	Signature	Date (day, month, year)

Appendix F

Patient Invitation Letter

Dear Avera Care Coordination Patient:

As a patient in the Avera Care Coordination program, you have been identified as being eligible to participate in a research study for a blood test that can assist your physician in improving your care through medication management. **The test would be available to you at no cost.**

Rather than taking a medication and waiting to see if it works, this test provides information on how your body will process and use medications, as well as how the medications you currently take interact with each other. Recommendations can then be made to your care team as to what medications may work best for you.

In order to enroll in this study, you will need to do the following:

- **Read and sign an Informed Consent Document.** This document explains what your participation would include, any risks and benefits, and other information you may want to consider before participating in the study.
  DO NOT sign this document until you have had an opportunity to speak to staff about it.

- **Have your blood drawn at an Avera McKennan or other Avera facility laboratory.** If you meet eligibility criteria and sign the Informed Consent Document, study staff will deliver a Genotyping Panel laboratory requisition to an Avera location of your choosing for the blood draw.

- **Answer a few questions on your past and present experiences with medications.** This information may help the research staff make additional correlations between genetics and medication responses.

If you do not receive a letter and information from the Avera Institute for Human Genetics in the next few days regarding this opportunity and would like to participate, please call (605) 322-3050 for more information or to see if you are eligib

APPENDIX G

December 18, 2015 Matthew Stanley, D.O.
AMG University Psychiatry associates 4400 W. 69th Street
Sioux Falls SD 57108

RE: Our Study #2014.080

Dear Dr. Stanley:

Meeting Date: 12/17/2015
Protocol Title: Title: Pharmacogenetic testing in an outpatient population of patients with Major Depressive Disorder or Depressive Disorder Not Otherwise Specified with Avera Medical Group Clinics

This is to inform you the Avera IRB renewed its approval of the above research study. The renewal is granted for an additional **12 months.**

The Effective date of the renewal is **12/17/2015:** The approval period will expire on **12/16/2016**
Our internal number: **8185**
The following items were reviewed:

- Continuing Review Report dated 3-Dec-2015
- Informed Consent dated 23-Jan-2015

All conditions for continued approval during the prior approval period remain in effect. These include, but are not necessarily limited to the following requirements:

- A stamped copy of the most current **Informed Consent Document** (as noted above) is included. No other consent documents should be used. Each subject must sign the approved ICD prior to initiation of any protocol procedures. The original signed informed consent document must be placed in each subject's medical/research chart. In addition, each subject must be given a copy of the signed consent document.
- All protocol amendments and changes to approved research must be submitted to the IRB and not be implemented until approved by the IRB except where necessary to eliminate apparent immediate hazards to the study subjects.

Please contact the Avera Dept of Human Subjects Protection (DHSP) at (605) 322-4706 if you have any questions about the terms of this approval.

Sincerely yours,

Sandra Ellenbolt

Sandra G. Ellenbolt, CIM, JD
Director, Department of Human Subjects Protection/IRB Chair

APPENDIX H

Table 33

Allele variation: *CYP 2D6 genotype*

Allele	Frequency	Percent
*1	3	2.4
*1/*1	14	11.3
*1/*10	3	2.4
*1/*2	28	22.6
*1/*4	10	8.1
*1/*41	13	10.5
*1/*6	1	.8
*1/*9	1	.8
*10	1	.8
*10/*41	2	1.6
*2	3	2.4
*2/*2	6	4.8
*2/*4	9	7.3
*2/*41	7	5.6
*2/*6	1	.8
*2/*9	2	1.6
*4/*4	5	4.0
*4/*41	3	2.4
*4/*9	2	1.6
*41	2	1.6
*41/*41	2	1.6
Total	118	95.2

Table 34

Allele variation CYP2C9gene

	Allele	Frequency	Percent
	*1/*1	70	56.5
	*1/*12	1	.8
	*1/*2	29	23.4
	*1/*23	1	.8
	*1/*3	13	10.5
	*2/*2	3	2.4
	Total	117	94.4
Missing	666	7	5.6
Total		124	100.0

Table 35

Allele variation CYP3A4gene

	Allele	Frequency	Percent
	*1*1	1	.8
	*1/*1	104	83.9
	*1/*1,1/*10, *10/*10	1	.8
	*1/*22	10	8.1
	*3/*11	1	.8
	Total	117	94.4
Missing	666	7	5.6
Total		124	100.0

Table 36

Allele variation CYP2C19gene

	Allele	Frequency	Percent
	*1/*1	48	38.7
	*1/*17	33	26.6
	*1/*2	2	1.6
	*1/*2A	15	12.1
	*1/*2B	1	.8
	*1/*8	1	.8
	*17/*17	6	4.8
	*2A/*17	7	5.6
	*2A/*2A	2	1.6
	*2B/*17	2	1.6
	Total	117	94.4
Missing	666	7	5.6
Total		124	100.0

Table 37

Allele variation CYP1A2gene

	Allele	Frequency	Percent
	*1A/*1A	14	11.3
	*1A/*1F	41	33.1
	*1B/*1B	1	.8
	*1B/*1F	1	.8
	*1B/*1L	1	.8
	*1B/*1P	1	.8
	*1f/*1F	1	.8
	*1F/*1F	54	43.5
	*1F/*1K	1	.8
	*1L/*1L	1	.8
	1F/*1L	1	.8
	Total	117	94.4
Missing	666	7	5.6
Total		124	100.0

Table 38

Allele variation CYP2B6gene

	Allele	Frequency	Percent
	*1/*1	33	26.6
	*1/*11	1	.8
	*1/*15	2	1.6
	*1/*2	7	5.6
	*1/*22	1	.8
	*1/*5	21	16.9
	*1/*6	29	23.4
	*1/*7 or *5/*6	1	.8
	*1/*7, *5/*6	1	.8
	*1/*7,*5/*6	2	1.6
	*1/*7,*5/*69	1	.8
	*1/7, *5/*6	1	.8
	*2/*5	1	.8
	*2/*6	4	3.2
	*4/*5	1	.8
	*5/*5	1	.8
	*5/*6	1	.8
	*6/*14	1	.8
	*6/*15	1	.8
	*6/*6	7	5.6
	Total	117	94.4
Missing	666	7	5.6
Total		124	100.0

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