EFFECTS OF INDIVIDUAL CHARACTERISTICS AND SYMPTOMS ON PHYSICAL FUNCTION IN PERSONS WITH LUMBAR DEGENERATIVE CONDITIONS

By

Teri Lynn Holwerda

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Nursing-Doctor of Philosophy

2014

ABSTRACT

EFFECTS OF INDIVIDUAL CHARACTERISTICS AND SYMPTOMS ON PHYSICAL FUNCTION IN PERSONS WITH LUMBAR DEGENERATIVE CONDITIONS

By

Teri Lynn Holwerda

Background/Significance: Back pain affects 80 percent of persons at some point in their lives. Lumbar disc degeneration, stenosis and facet joint degeneration have been associated with low back pain. Degenerative changes increase with age. Genetic influences affect the spinal degenerative process and the experience of pain. The symptoms that accompany degenerative spinal conditions include back pain, leg pain, numbness and weakness. Low back and leg pain are associated with reduced physical function. Physiological, situational and psychological patient characteristics influence physical function in degenerative lumbar conditions. These characteristics include genotype, BMI, smoking, age, employment status, insurance type, worker's compensation claim and depression. **Problem**: Little is known about the interaction among patient characteristics and symptoms and the outcome of physical function for persons with lumbar spinal degeneration. **Purpose:** This study was undertaken to explore the contribution of patient characteristics and symptoms to the outcome of physical function in a population of individuals experiencing lumbar degenerative conditions. **Specific Aims:** 1) Determine the contribution of physiological (BMI, sex, age, smoking status), situational (employment status, worker's compensation claim, insurance type), and psychological (depression) factors in persons receiving non-surgical interventions for degenerative lumbar conditions to symptoms and physical function, 2) Develop a predictive model for the outcome of physical function in persons receiving non-surgical interventions for lumbar degenerative

conditions, using symptoms (back and/or leg pain, numbness, and weakness) and physiological, situational, and psychological patient factors, and 3) Explore the impact of the physiological factor genotype (disc structural genes and pain genes) on symptoms (back and/or leg pain, numbness, and weakness) and on physical function in persons experiencing lumbar degenerative conditions. **Instruments:** Physical function is the primary outcome, measured by the physical function subscale of the SF-36 and the Oswestry Disability Index, (ODI). **Methods:** Using a cross-sectional, observational design, 163 subjects were randomly selected from an existing database of completed SF-36 and ODI questionnaires at a tertiary outpatient spine center. Data on symptoms and physiological, situational, and psychological characteristics were obtained from the medical record. A random subset of 28 subjects consented to provide saliva samples for genotyping. **Results: Aim 1:** Smoking, having Medicaid insurance or no insurance were negatively associated with the symptom pain VAS. Higher BMI and smoking were associated with worse ODI scores, while having Commercial insurance or Medicare was associated with better ODI scores. Higher BMI, smoking, older age, and having Medicaid insurance were associated with worse SF-36 physical function subscale scores. **Aim 2:** Higher BMI, smoking, higher pain VAS and numbness predicted 35% of the variance in ODI scores. Higher BMI, older age and the symptom higher pain VAS predicted 26% of the variance in SF-36 physical function subscale scores. **Aim 3:** No genotype was significantly associated with symptoms. *OPRM1* A/A carriers had significantly worse physical function scores than those with */G alleles. **Implications:** This study is an important step in identifying the combination of patient characteristics, (including genotype) and symptoms that impact physical function in this population, in order to tailor interventions to preserve physical function.

ACKNOWLEDGEMENTS

My only comfort in life and death is that I belong to my faithful savior, Jesus Christ. My hope is in Him.

Over the past five years, I have received assistance from many individuals. Dr. Debra Schutte has been a valuable mentor, friend and role model. Her sage and patient counsel have steadied my focus.

I would like to thank the Chair of my Dissertation Committee, Dr. Barbara Given. I have benefitted from her knowledge and experience as a nurse researcher. I thank her for holding me to a high standard. I would also like to thank the members of my Dissertation Committee, Dr. Amy Hoffman, Dr. Barbara Smith, Dr. Paul Stephenson and Dr. Daniel Vaughn. I am indebted to Amy for her symptom expertise and kind encouragement. I thank Barbara Smith for her invaluable critique of my writing, and Dan for his expertise in physical function and for sharing his priceless skills as a journal editor. I am thankful for the contagious enthusiasm Paul has for statistical analysis. Because of his patient guidance, I was enthralled by the revelations of my data, even in the last stages. I survived because of all of you. I am also grateful to Dr. Alan Davis, Director of Research at Grand Rapids Medical Education Partners, for his kind assistance.

I am indebted to my family, husband BJ, and daughters Andrea (and Kyle) and Olivia for their unwavering support and encouragement. Words cannot express how much I love you all.

I could not have completed this work without the generous support in the form of a dissertation small grant from the Saint Mary's Foundation. I am also grateful for the

financial support I received from the College of Nursing and the Graduate School, specifically the John F. Dunkel Memorial Endowed Scholarship, College of Nursing Fellowships, College of Nursing Scholarships, a Graduate School Fellowship, and a Dissertation Completion Fellowship.

Last, and not least, I would like to thank the staff of the Research & Innovation department at Mercy Health Saint Mary's for their guidance and direction. Their positive approach kept me energized.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

Introduction

Background and Significance

Back pain and the symptoms that accompany lumbar degenerative conditions are a highly prevalent and important health problem. More than 20% of adults responding to the 2009 National Health Interview Survey experienced back pain in the three months prior to the survey (National Center for Health Statistics). Back pain affects about 80 percent of persons at some point in their lives (Healthy People 2020, 2012). Individuals with back pain are likely to continue to have recurrent episodes of back pain over time and two to ten percent of back pain is chronic (Healthy People, 2020, 2012). Approximately one-third of persons develop persistent low back pain one year after an acute pain episode (Von Korff & Saunders, 1996).

Though most episodes of back pain are self-limiting, back pain can affect physical function (Carey, et al., 1996; Thomas et al., 1996; Samartzis et al., 2011; Chung-Wei, et al., 2011). In fact, back pain is a frequent reason for visits to physicians, Emergency Departments, and hospitalizations (Healthy People 2020, 2012). Conditions involving the low back comprise the fifth most frequent cause of hospitalization and the third most common reason for surgery (Healthy People 2020, 2012). Back pain is the second leading cause of work absence, after the common cold (Healthy People 2020, 2012).

There are many causes for back pain. Degenerative conditions involving the intervertebral disc have been identified as one cause of low back pain (Cheung, Samartzis, Karppinen & Luk, 2012; Freemont, 2009; Livshits, et al., 2011; Takatalo et al., 2011). The prevalence of disc degeneration is estimated to be as high as 40% for individuals under the age

of 30 (Cheung, et al., 2009). By age 50, the prevalence rises to 60-90% (Cheung, et al, 2009; Kalichman, Kim, Li, Guermazi & Hunter, 2010).

Back pain is not the only problematic symptom of lumbar degeneration. As degeneration progresses, the combination of facet joint arthritis and disc height reduction can produce changes that decrease the diameter of the canal and neuroforamen, which can contribute to spinal nerve symptoms of limb pain, numbness, tingling and weakness (Genevay & Atlas, 2010).

The population of the United States is aging. Current estimates predict that by the year 2015, 27% of the population will be age 55 or older and 14.4% of the population will be aged 65 or older (U.S. Census Bureau, 2012). Therefore, the prevalence of degenerative conditions affecting the spine is anticipated to increase as well. More persons will develop progressive degenerative spinal changes and therefore be at risk for the development of the symptoms that accompany degenerative spinal conditions.

Factors Affecting Outcome in Persons with Lumbar Degenerative Conditions

Patient characteristics and their influences on outcomes for persons experiencing lumbar degenerative conditions have been studied. Several situational, psychological and physiological patient characteristics have been shown to affect physical function outcomes for persons experiencing lumbar degenerative conditions. The physiological factors (defined as biologic and physical features possessed by the individual) genotype, obesity, smoking and age have been shown to influence lumbar degeneration and low back pain. The situational factors (defined as features that are outside the individual that may influence health status) employment status, worker's compensation claim and insurance type can affect the physical function outcome of non-surgical treatments for individuals with lumbar degenerative conditions. The psychological factor (defined as mental state or mood) depression has been associated with greater pain and

worse physical function in persons with lumbar degenerative conditions. Symptom experience can influence outcome, and in general, the worse the symptom experience, the more negative the impact on the outcome of physical function.

Purpose of the Study

The purpose of this cross-sectional observational study is to explore the contributions of patient characteristics (including genotype), and symptoms to the outcome of physical function in a population of individuals experiencing lumbar degenerative conditions. The goal is to begin to develop a method to identify persons with lumbar degenerative conditions at increased risk of experiencing decreased physical function, in order to tailor interventions or adjust treatment approaches to improve outcomes for the entire population.

Specific Aims

Aim 1: To determine the contribution of physiological (BMI, sex, age, smoking status), situational (employment status, worker's compensation claim, insurance type), and psychological (depression) characteristics in persons receiving non-surgical interventions for degenerative lumbar conditions to symptoms and physical function.

Aim 2: Develop a predictive model for the outcome of physical function in persons receiving non-surgical interventions for lumbar degenerative conditions, using symptoms (back and/or leg pain, numbness, and weakness) and physiological, situational, and psychological patient characteristics.

Exploratory Aim 3: Explore the impact of the physiological characteristic genotype (disc structural genes and pain genes) on symptoms (back and/or leg pain, numbness, and weakness) and on physical function in persons experiencing lumbar degenerative conditions.

The expected outcome from this research will be knowledge about the symptom experience in persons experiencing degenerative lumbar conditions, the interaction of symptoms with patient factors influencing the outcome of physical function in this population, and the development of predictive models to identify populations at risk for worse physical function. As a result of this proposed investigation, it is expected that predictions based on symptoms and patient factors will result in improved outcomes for persons with lumbar degenerative conditions.

Outcome of Interest

Physical Function Definition

Physical function--defined as an individual's ability to fully perform in the various physical roles in their lives, to accomplish ADLS, to work, carry out daily tasks for self and significant others, to be mobile, and maintain leisure physical activities--is a requisite part of overall quality of life (Rejeski & Mihalko, 2001; Ferrans, et al., 2005). Physical function is foundational to the ability to operationalize roles (Lenz, et al., 1997), forming the basis for an individual's ability to accomplish the activity required to provide for basic needs, fulfill life roles, and maintain health and well-being (Leidy, 1994; Hoffman, et al., 2009).

Decline in physical function with aging can negatively affect cognitive function (Eggermont, Milberg, Lipsitz, Scherder & Leveille, 2009). Decline in physical function is also associated with increased mortality and greater risk of disability (Cawthon et al., 2011; Gillum & Obisesan, 2010).

Physical Function in Persons with Lumbar Degenerative Changes

Lumbar spine degenerative changes can cause alterations in physical function. Low back pain is associated with reduced physical function in younger and older adults (Samartzis et al., 2011; Chung-Wei, et al., 2011). The presence of chronic low back pain and leg pain is associated with greater disability and less optimum health (Prins, van der Wurff & Groen, 2013). Lumbar degenerative changes increase with age (Bogduk, 2012).

Lumbar Degeneration

Anatomic Changes

Manifestations of lumbar degeneration include decreased height of the intervertebral disc, bulging of the outer layer (annulus) of the intervertebral disc, facet joint hypertrophy, thickening of the ligamentum flavum, and stenosis of the central canal, lateral recesses, and neuroforamen (Chokshi, Quencer & Smoker, 2010; Genevay & Atlas, 2010; Varlotta et al., 2011). As the intervertebral disc degenerates, more stress is placed on the facet joints, contributing to arthritis, joint space narrowing, erosion of the joint, hypertrophy and the development of bone spurs (Kalichman & Hunter, 2007; Modic, 2007). Facet joint degenerative changes and decreased disc height are associated with hypertrophy and buckling of the ligamentum flavum, which then encroaches on the spinal canal (Altinkaya, Yildirim, Demir, Alkan & Sarica, 2011; Chokshi, Quencer & Smoker, 2010; Genevay & Atlas, 2010). Lumbar facet joints and the posterior annulus of the intervertebral disc are enervated (Falco et al., 2012; Moon et al., 2012; Van Zundert, Vanelderen, Kessels & van Kleef, 2012). Lumbar intervertebral disc degeneration, lumbar stenosis and facet joint degeneration have been associated with low back pain (Cheung et al., 2009; Cohen & Raja, 2007; Kalichman, Kim, Lee, Guermazi & Hunter, 2010; Moon, et al., 2012; van Kleef et al, 2010).

Economic Problem

Estimates of the cost of low back pain in the United States vary widely, but sources suggest the costs range from $50-625 billion per year (Dagenais, S., Caro, J. & Haldeman, S. 2008; Healthy People 2020). Many treatments are available for lumbar spinal conditions, ranging from physical therapy to surgery. Wide variations in the approach to diagnosis and treatment exist. Complex surgery rates for lumbar stenosis are on the rise, and significant geographical differences in surgical rates have been identified (Deyo, Mirza, Martin, Kreuter, Goodman & Jarvik, 2010; Weinstein, Lurie, Olson, Bronner & Fisher, 2006).

The charges for lumbar fusion surgery in the U.S. increased nearly eight-fold between 1998 and 2008, rising from 4.3 billion to 33.9 billion over that decade (Rajaee, Bae, Kanim & Delamarter, 2012). Rising surgical costs have been fueled by increased instrumentation, biologics, and device usage (Deyo, Mirza, Martin, Kreuter, Goodman & Jarvik, 2010; Weinstein, Lurie, Olson, Bronner & Fisher, 2006). At best, overall success for lumbar spinal surgical procedures has been estimated to be fifty percent; 25% persons undergoing spinal surgery experience no improvement at all (Block, Gatchel, Deardorff & Guyer, 2003). Costs associated with non-surgical treatment for lumbar disc herniations are also substantial (Daffner, Hymanson & Wang, 2010).

Diagnostic and Treatment Variation

There is considerable variability in the classification of low back pain, given the many different sources of pain in the lumbar spine (Fairbank, et al 2011). Low back pain is felt to be a heterogenous condition with clinically distinct subgroups and different pain generators (Fourney, et al., 2011). Because of the lack of consensus on the source and classification of low back pain, there is variability in the recommendations for treatment (Benoist, Boulo & Hayem, 2012;

Cheng, et al., 2011; Choma, Schuster, Norvell, Dettori & Chutkan, 2011; Pereira et al., 2012). There is therefore a need to begin to classify subgroups of patients whose profiles suggest a higher risk for impairment of physical function.

Genetics and Lumbar Degeneration

The role of genetics in the development of lumbar degenerative conditions has been of great interest in recent years. Hereditary and biological mechanisms contributing to disc degeneration have been identified (Zhang, Sun, Liu & Guo, 2008). Heritability is the variance in phenotype attributable to genetic factors (Holliday & McBeth, 2011). The heritability of lumbar intervertebral disc degeneration has been estimated to be 29-61% (Battie, Videman, Levalahti, Gill & Kaprio, 2008; Kalichman & Hunter, 2008). Lumbar disc degeneration is now considered to be a complex process with both genetic and environmental contributors, and investigators have identified several candidate genes that may be involved in the lumbar degenerative process (Hadjipavlou, Tzermiadianos, Bogduk & Zindrick, 2008). Genes related to the integrity of the intervertebral disc and genes related to the breakdown of disc components are among those implicated in the process of disc degeneration.

In summary, lumbar disc degeneration is one cause of low back pain. Once considered a consequence of mechanical stress, disc degeneration is now thought to be a complex process related in part, to genetic as well as environmental factors.

Genetics and the Experience of Low Back Pain

Pain, like lumbar disc degeneration, is an etiologically complex phenomenon, likely influenced by genetic and environmental factors. In fact, much is known about the genetics of pain. For example, twin studies have demonstrated the heritability of the symptom of back pain. Estimates of the heritability of low back pain ranges from 30-68% (Battie, Videman, Levalahti,

Gill & Kaprio, 2007; Hartvigsen et al, 2009; MacGregor, Andrew, Sambrook & Spector, 2004). In addition, several genes have been implicated in the variability of the experience of pain, among them, genes that code for opioid receptors and *catechol-o-methyltransferase*. Variability in these genes has been implicated in an increased experience of pain, increased susceptibility to pain, and differences in analgesic requirements for pain states (Argoff, 2010; Dai, F. et al., 2010; Kim & Schwartz, 2010; Kleiber, et al., 2007; Miaskowski, 2009).

In summary, the experience of pain as a symptom in general is now known to be related in part, to genetic factors. There is also accumulating evidence that pain genetics influence pain states specifically in degenerative lumbar spinal conditions. And, while more is known regarding genetic influences on the degenerative process involving lumbar intervertebral discs and the genetic influences on the symptom of low back pain, there is a need for studies examining the combined effects of pain and disc degeneration genotype on the symptoms of lumbar degeneration and the outcome of physical function in this population.

Patient Characteristics and Effects on Various Outcomes in Lumbar Degeneration

Patient characteristics and their influence on outcomes for persons experiencing lumbar degenerative conditions have been studied. Several situational, psychological and physiological patient characteristics have been shown to affect aspects of pain and functional outcomes of persons experiencing lumbar degenerative conditions. These outcomes have included functional status, ability to return to work, intensity of the experience of pain and the development of chronic pain.

The relationships between patient situational characteristics and surgical spinal outcomes are well-documented. Patients receiving Worker's Compensation had worse functional status after surgical and non-surgical treatments for spine conditions (Anderson, Subach, & Riew,

2009; Atlas, Chang, Kamman, Keller, Deyo, & Singer, 2000; Burnham, et al, 1996; Voorhies, Jiang & Thomas, 2007; Yang, Lowe, de la Harpe & Richardson, 2010). Unemployment status has a negative impact on post-treatment outcomes for persons undergoing surgical or non-surgical treatments and those working pre-operatively were ten times more likely to be working post-operatively after lumbar fusion surgery (Anderson, Schwaegler, Cizek & Leverson, 2006; Burnham et al., 1996; Silverplats et al., 2010; Zieger, et al., 2011).

The psychological characteristic of depression can contribute to the development of chronic low back pain, can be a predictor of new pain episodes, and is negatively correlated with outcome and return to work after surgery for lumbar herniated disc (Carragee, Alamin, Miller & Carragee, 2005; Jarvik, Hollingworth, Heagerty, Haynor, Boyko, & Deyo, 2005; Kohlboeck et al, 2004; Pincus, Burton, Vogel & Field, 2002; Trief, Grant & Fredrickson, 2000). Greater levels of depression are associated with more functional disability in persons with chronic low back pain (Feirerra & Pereira, 2013). Persons with low back pain have been found to have higher rates of depression than those without low back pain (Bener et al., 2013). Not only are depression and low back pain significantly correlated, but depression and anxiety are predictors of greater low back pain intensity (Mok & Lee, 2008; Tetsunaga et al., 2013).

Several physiological characteristics have been shown to contribute to the development of low back pain. Obesity is a risk factor for low back pain (Heuch, Hagen, Heuch, Nygaard & Zwart, 2012; Shiri, Karppinen, Leino-Arjas, Solovieva & Viikari-Juntura, 2010; Shiri, et al., 2008). Obesity was one of the factors found to increase the costs associated with lumbar interbody fusion (LaCaille, DeBerard, LaCaille, Masters, & Colledge, 2007). Smokers have a higher incidence of back pain than non-smokers (Shiri, Karppinen, Lein-Arjas, Solovieva, & Viikari-Juntura, 2010).

The Effect of Symptoms on Outcomes

Symptoms are subjective phenomena that indicate a change in health or normal function (Dodd, et al., 2000; Fu, LeMone, & McDaniel, 2004; Farrar, Berlin, & Strom, 2003; Fu, McDaniel, & Rhodes, 2007). Symptom experience can influence outcome, and in general, the worse the symptom experience, the more negative the impact on outcome.

Lumbar degenerative conditions can be a cause of the symptoms of low back pain and lower limb pain, numbness, tingling and weakness. Low back pain and other symptoms related to lumbar degenerative conditions can reduce physical function. The consequences of symptoms in general include impact on adjustment to illness, quality of life, functional status, psychological state, survival, and disease progression (Armstrong, 2003). The consistent finding is that the worse the symptom experience, the poorer the outcomes, across many health conditions. (Edward, et al., 2007; Hammer, Howell, Bytzer, Horowitz, & Talley, 2003; Wilson, Robinson, & Turk, 2009).

Identification of subgroups of patients who experience symptoms with greater severity may alert nurses to persons at risk for poorer outcomes (Miaskowski, et al. 2006). Nurses can help patients identify and understand the cause for their symptoms, thereby leading to prompt intervention and more effective coping through behavior interventions (Heidrich, Egan, Hengudomsub, & Randolph, 2006). Identification of those priority symptoms that exert a negative effect on other symptoms enable nurses to target intervention on the priority symptom, thereby reducing the severity of the other symptoms and improving outcomes (Hoffman, von Eye, Given, Given, & Rothert, 2009). Lumbar degenerative conditions are an expensive and highly prevalent health condition which can lead to diminished physical function. Optimizing

physical function, in the context of lumbar degenerative conditions, is an important nursing concern.

Knowledge Gap

While multiple patient factors have been found to independently influence physical function outcomes for persons experiencing lumbar degenerative conditions, little is known about the interaction of individual patient characteristics, genotype, and symptoms and their impact on physical functioning in persons with lumbar spinal conditions receiving non-surgical care. The gap in knowledge regarding symptoms and patient factors as predictors of physical function in this population limits caregiver's ability to tailor interventions designed to improve or preserve physical function. Identifying those at risk for poor outcomes would allow for adjusting treatment approaches to improve outcomes in this population.

Identification of the relationships between these factors could assist in the accurate prediction of those patients at risk for sub-optimal outcomes from a non-surgical approach to treatment for lumbar spinal conditions. Alternate care models could then be developed to improve the outcomes of at-risk populations. The long term goal is to develop a predictive model for outcome in persons with lumbar spinal conditions being treated non-surgically based on patient characteristics, genetics and symptoms. Nurses are unique among all health professionals in their holistic focus in diagnosing and treating human responses to health conditions. There is no literature that examines patient factors (including genotype) and symptoms and their effects on the outcome of physical function in adults experiencing lumbar degenerative conditions. This study addresses a serious gap in knowledge regarding the multiple factors that contribute to worse physical function outcomes, thus providing important data for personalizing care for patients experiencing lumbar degenerative conditions.

A better understanding of the role of genes involved in the experience of pain and the genes involved in disc degeneration may help identify those at risk for not only disc degeneration, but also at risk for greater pain and disability. Exploration of genetic and patient factors can identify individuals at risk for poorer outcomes from spinal interventions. Early, tailored interventions to control pain and prevent chronicity could be implemented when these risk factors are known. As scientists learn more about the links between the genes involved in disc degeneration and environmental factors, nursing interventions can be developed for populations at risk, to reduce pain and disability.

In summary, this study aims to add to nursing science by examining simultaneously the physiological, situational and psychological individual characteristics that affect physical function for persons experiencing lumbar spinal degenerative conditions. Moreover, the incorporation of symptoms in combination with individual characteristics and their influence on physical function brings a uniquely nursing perspective to a condition that affects 80% of persons in their lifetime. Last, the incorporation of genotyping as a relevant physiological characteristic in this study is innovative and may lead to further insight into personalizing care for persons experiencing lumbar degenerative conditions.

CHAPTER II

Conceptual Framework

The framework organizing the approach to this inquiry is The Theory of Unpleasant Symptoms, (Lenz, Gift, Pugh, & Milligan, 1995; Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The Theory of Unpleasant Symptoms (TOUS) is a multi-dimensional, dynamic, middle-range theory that is unique in its consideration of multiple symptoms occurring simultaneously that catalyze each other. The TOUS is a middle-range theory and is therefore more specific than a grand theory. Middle-range theories are less abstract and are focused more on specific phenomena (Fawcett, 2005). Middle-range theories are more directly useable for nursing practice application (Peterson & Bredow, 2009; Smith & Liehr, 2008).

The TOUS was developed after nursing clinicians, separately working on the symptoms of dyspnea and fatigue, recognized similarities between their conceptualizations regarding the context in which these symptoms occurred and the effect these symptoms had on performance (Gift, 2009). Knowing that there were similar activities focused on the symptom of pain, they set out to craft one model that could guide the understanding and management for many symptoms. In the first iteration of the model, three categories of factors were believed to influence the predisposition to or manifestation of an unpleasant symptom (Lenz, Suppe, Gift, Pugh, & Milligan, 1995). These categories were: physiological, situational and psychological. These factors were specifically conceptualized to begin to identify interventions to ameliorate or reduce the impact of fatigue. The authors believed that by identifying the factors that contributed to the symptoms, interventions aimed at modifying these factors would reduce the symptoms (Lenz, Suppe, Gift, Pugh & Milligan, 1995). Symptoms were conceptualized as having variable duration, intensity, quality, and distress (Lenz, Suppe, Gift, Pugh, & Milligan, 1995).

Symptoms influence performance, which includes functional status, cognitive functioning, and physical performance (Lenz, Suppe, Gift, Pugh, & Milligan, 1995). The original model presented a linear depiction of the variables.

Work continued on the model over the next two years, and in 1997, the authors published their updated Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The new model went from a linear, unidirectional depiction of variables to a sophisticated, interactive, dynamic feedback loop incorporating antecedents, (or influencing factors), the symptoms themselves (with recognition that many symptoms can be experienced at once, and that they interact with and catalyze one another), and the outcome, performance (which in turn, affects how symptoms are experienced and the influencing factors). The propositions of the TOUS describe how each concept relates to the others. The antecedent factors may interact together, antecedent factors interact in their influence on symptoms, symptoms may influence the effect antecedent factors have on performance, antecedent factors and symptoms together influence cognitive and physical performance and performance can have reciprocal effects on symptoms and antecedent factors (Lenz, Pugh, Milligan, Gift & Suppe, 1997). The outcome of performance includes both functional and cognitive features (Lenz, Pugh, Milligan, Gift & Suppe, 1997). Physical function is the performance outcome of interest in this study. (See Figure 1 for the Theory of Unpleasant Symptoms with Study Variables).

Antecedent factors are described in the TOUS update (1997). Physiological factors include normally functioning body systems, the presence of trauma, or the existence of pathology (Lenz, Pugh, Milligan, Gift & Suppe, 1997). Psychological factors include mental state or mood, affective reaction to illness, and uncertainty about the symptoms and their meaning (Lenz, Pugh, Milligan, Gift & Suppe, 1997). Situational factors include marital and employment status, access to health care, diet, exercise and social support (Lenz, Pugh, Milligan, Gift & Suppe, 1997).

The defining attributes of physical function are fairly explicit in this model. Physical function, or "functional performance", includes physical activity, activities of daily living, social activities, work, and "other role related tasks" (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Greater or more severe symptoms can reduce functional performance, role performance, and "physical performance capabilities" (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Decreased levels of performance in this dynamic, reciprocal model can affect symptoms and the physiologic, psychological, and situational antecedent factors (Lenz, Pugh, Milligan, Gift, & Suppe, 1997).

The TOUS is circumscribed and limited in scope and addresses the phenomena of symptoms, how they influence one another, how symptoms are influenced by antecedent factors, and how these phenomena influence performance. Each concept in the TOUS interacts together in a continuous feedback loop. The authors claim that the TOUS is parsimonious for proposing that the same antecedent factors could influence many symptoms and that a single intervention has the potential for alleviating more than one symptom (Lenz, Pugh, Milligan, Gift & Suppe, 1997). The concepts and propositions in the TOUS are stated concisely. Even though there are

multiple relationships between the concepts of the model, they are portrayed in an economical way.

The nursing metaparadigm concepts addressed by the TOUS include: an aspect of health (cognitive and physical function), human beings (their symptoms and the physiological and psychological features they possess), and their environment (the situational factors that influence their symptoms and function). Lenz, Suppe, Gift, Pugh and Milligan (1995) were clear that the early focus on antecedent factors and their influence on symptoms were for the purpose of identifying interventions. Interventions could then be developed to modify the antecedent factors found to influence symptoms (Lenz, Suppe, Gift, Pugh & Milligan, 1995). Implicit in the model is that the goal of nursing is to enhance function. In the TOUS update, Lenz, Pugh, Milligan, Gift and Suppe (1997) describe how interventions can be individualized by using the antecedent factors and patterns of symptoms unique to the individual. The authors do state that by controlling one symptom, the effect of many symptoms and function may be enhanced (Lenz, Pugh, Milligan, Gift & Suppe, 1997).

Symptoms are the central focus of the model. Symptoms can occur together because of a single event, such as surgery, or one symptom can precede another. Although symptoms may be different, most symptoms share the dimensions of intensity, quality, duration and distress (Lenz, Pugh, Milligan, Gift & Suppe, 1997). Intensity refers to the amount, strength or severity of a symptom. Quality is the way in which a symptom is manifested, and is reflected in the words used by the individual to describe its nature. Symptom quality also includes the location of the symptom. Quality aspects are felt to be specific to a given symptom, and this symptom feature may be difficult for individuals because ability to recognize and describe a symptom may vary (Lenz, Pugh, Milligan, Gift & Suppe, 1997). Symptom duration provides a time element to the

symptom experience and includes the frequency, timing and length of the symptom. Distress reflects the degree to which an individual is bothered by a symptom. How much an individual is bothered by a symptom can determine help-seeking. Individuals vary in their estimations of how bothered they are by the same symptom. The symptom distress dimension contributes most to quality of life (Lenz, Pugh, Milligan, Gift & Suppe, 1997). Symptoms are conceptualized to catalyze each other, with the effect of greater impact of symptoms on function. Lenz, Pugh, Milligan, Gift and Suppe (1997) assert that symptoms occurring simultaneously have a multiplicative, rather than an additive effect on each other. Interventions to manage symptoms should be based on the dimensions of the symptom.

While the specific activities of nurses are not explicitly portrayed in the TOUS, the authors do state that the purpose for development of the model was to help nurses identify individualized interventions through delineation of the antecedent factors and their effects on the symptoms experienced by the patient (Lenz, Suppe, Gift, Pugh & Milligan, 1995; Lenz, Pugh, Milligan, Gift & Suppe, 1997). The TOUS provides for a method to discern the dimensions of symptoms and identify the antecedent factors that contribute to them across a range of clinical conditions. This allows the nurse to tailor interventions appropriate to the situation. However, Brant, Beck and Miaskowski (2010), in their comparison of middle-range theories addressing symptoms, contend that there is no consideration for intervention in the TOUS, or for resolution of a symptom.

The special contribution this middle-range theory makes is its recognition that most individuals experience more than one symptom, and that the experience of symptoms may be multiplicative, rather than additive (Lenz, Pugh, Milligan, Gift & Suppe, 1997). The conceptualization of multiple symptoms occurring simultaneously represents the reality of

clinical care. The TOUS has even been used outside the discipline of nursing (Motl & McAuley, 2009).

The TOUS has been criticized for lack of clarity of what constitutes physiological, situational and psychological antecedent factors (Brant, Beck & Miaskowski, 2010). A lack of clear differentiation between antecedent factors and symptoms in the TOUS has also been noted. In a qualitative study using the TOUS in a population of patients and care-givers with Alzheimer Disease (AD), the authors found utility and fit in the model's antecedent factors, multiple simultaneous symptom experience, interaction between symptoms, interaction between antecedent factors and symptoms and interaction between antecedent factors in AD (Hutchinson & Wilson, 1998). However, they noted blurred boundaries and overlap between antecedent factors and symptoms—there was lack of clarity regarding whether study variables like anxiety and depression were psychological antecedent factors or symptoms. However, in the first iteration of the model, the authors explicitly state that depression and fatigue are conceptualized to be psychological antecedent factors (Lenz, Suppe, Gift, Pugh and Milligan, 1995). Hutchinson and Wilson (1998) concluded that the TOUS was useful in describing and assessing the complexity and relationships between multiple antecedent factors, symptoms and performance outcomes in AD. In fact, most studies utilizing the TOUS conceptualize depression as an antecedent factor (Corwin, Klein & Rickelman, 2002; Liu 2006; Redeker, Lev & Ruggiero, 2000; Rychnovsky, 2007; So et al., 2012). Only one study conceptualized depression as a symptom (Motl & McAuley, 2009).

The model has been found to be useful in demonstrating that multiple symptoms occurring together affects outcome (Gift, Jablonski, Stommel & Given 2004; Liu, 2006; Motl & McCauley 2000; Myers 2009). Multiple antecedent factors have also been shown to affect the

experience of one symptom (Corwin, Klein & Rickelman 2002; Woods, Kozachik & Hall, 2010). Antecedent factors have also been shown to affect symptoms, which in turn, affects function (Hoffman, von Eye, Gift, Given & Given, 2009). However, not all studies provide support for the influence of antecedent factors on symptoms and the combined effect on function (Redeker, Lev & Ruggiero, 2000).

The TOUS is a testable model. Many nursing and some non-nursing studies have tested the propositions of the TOUS. Though not all of the propositions of the TOUS have been supported, many studies have explored the influence of antecedent factors on symptoms, the influence of symptoms on function and multiple symptoms occurring together influencing outcome. In the 1997 update, Lenz, Pugh, Milligan, Gift and Suppe offer examples of instruments that capture symptom dimensions. The McGill Pain Questionnaire and the Fatigue Symptom Checklist are provided as examples of instruments used to measure symptom quality. A Visual Pain Analog can measure symptom intensity. Both quantitative and qualitative methods should be considered in the measurement of symptoms, and the authors recommend "multidimensional, multifactorial measurement procedures" (Lenz, Pugh, Milligan, Gift & Suppe, 1997).

Cognitive and physical performance is not the only outcomes examined using the TOUS. Some authors have inserted quality of life, self-efficacy and depression as the outcome. Some authors have placed self-efficacy as a mediator between symptoms and outcome, but have not defined self-efficacy as a psychological antecedent factor.

In an analysis of the usefulness of the TOUS to guide the evolving understanding of symptom burden in irritable bowel syndrome, the authors concluded that the TOUS had utility to guide symptom research in this disease (Farrell & Savage, 2009). Myers (2009) compared the

TOUS and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function for guiding research, and found the TOUS to be advantageous for its inclusion of multiple co-occurring symptoms and its interrelationships between antecedent factors and symptoms. The TOUS was felt to be a useful way for nurses to place symptoms in the context of antecedent factors that influence them in the study of patients undergoing bariatric surgery (Tyler & Pugh, 2009).

The TOUS has been used widely to guide research across a number of populations, although no studies were identified involving patients with spinal conditions that utilized the TOUS as an organizing framework. There were several studies using the framework in populations experiencing fatigue and cancer (Corwin, Brownstead, Barton, Heckard & Morin, 2005; Corwin, Klein & Rickelman, 2002; Gift, Jablonski, Stommel & Given, 2004; Hoffman, von Eye, Gift, Given & Given, 2009; Liu, 2006; Motl & McAuley, 2009; Redeker, Lev & Ruggiero, 2000; Reishtein, 2004; Rychnovsky, 2007). Most studies have provided support for the propositions of the TOUS.

There is evidence for psychological antecedent factors influencing symptoms. Corwin, Brownstead, Barton, Heckard and Morin (2005) used post-partum depression as the outcome in a study to explore the factors predictive of this condition. Those women who were fatigued at post-partum day 14 also scored as significantly depressed at post-partum day 28.

Some evidence has been provided for the influence of antecedent factors on symptoms, which in turn, affects function. Using a secondary analysis of baseline data from two randomized controlled trials involving individuals undergoing chemotherapy for cancer, the authors set out to test the hypothesis that physical functional status can be predicted through patient factors, cancer-related fatigue, "other" symptoms, and perceived self-efficacy for fatigue

self-management in individuals with cancer (Hoffman, von Eye, Gift, Given & Given, 2009). Fatigue was the most severe and prevalent symptom, and was correlated with cancer-related fatigue severity. Younger age, female sex, and greater number of co-morbid conditions predicted greater cancer-related fatigue severity. Greater cancer-related fatigue severity predicted greater symptom severity, but the reverse was not demonstrated. Greater cancer-related fatigue severity predicted lower perceived self-efficacy for fatigue self-management, and greater perceived self-efficacy for fatigue self-management predicted greater physical functional status.

However, not all studies have confirmed the influencing relationship between antecedent factors on symptoms affecting function. Redeker, Lev and Ruggiero (2000) examined the symptoms of insomnia and fatigue and the psychological factors of depression and anxiety to determine their contribution to quality of life in a Chinese population undergoing chemotherapy. They found that depression had the greatest effect on quality of life, with the symptoms of insomnia and fatigue only accounting for 4% of the variance in quality of life. While they were able to demonstrate that depression explained most of the variance in quality of life, they were unable to demonstrate that psychological factors catalyzed symptoms to affect quality of life. In their critique of the utility of the TOUS, they questioned how to account for changing psychological factors like anxiety and depression, and called for more clarity regarding psychological factors (Redeker, Lev & Ruggiero, 2000). In a response following Redeker, Lev & Ruggiero's published study, Pugh, Milligan and Lenz (2000) acknowledged that different concepts could potentially fit as antecedent factors or symptoms, depending on the phenomenon under study. However, they contended that the study by Redeker, Lev and Ruggiero (2000) was

not a true test of the model, because it was used simply to correlate relationships proposed from a secondary analysis of data (Pugh, Milligan & Lenz, 2000).

Another study was unable to make the connection between antecedent factors, symptoms, and outcome (quality of life). Consistent with the purpose of the TOUS, hospitalized heart failure patients were studied to identify symptom clusters and factors contributing to the experience of these symptoms (Jurgens, et al., 2009). Using quality of life as an outcome measure, the authors discovered three symptom clusters explaining much of the variance in quality of life in hospitalized heart failure patients. Shortness of breath, fatigue and sleep problems as a cluster explained 46% of the variance in quality of life; depression, memory problems and worry as a cluster explained 13% of the variance. The symptom cluster of swelling, need to rest and dyspnea explained an additional nine percent of the variance in quality of life (Jurgens, et al. 2009). They were unable to demonstrate that the factors of co-morbid disease and age catalyzed the impact of these symptom clusters to affect quality of life.

There has been support for the influence of symptoms on physical function. Motl and McAuley (2009) studied patients with Multiple Sclerosis and the temporal relationship between symptoms and physical activity behavior six months later. They were able to demonstrate a predominant symptom cluster of fatigue, depression and pain, which had a strong and negative effect on physical activity behavior measured by accelerometry. They also explored whether the symptom cluster had a direct effect on physical activity behavior, or whether this effect was mediated by self-efficacy. They found that self-efficacy did not mediate this relationship. Curiously, as they were testing model fit, they conceptualized functional limitation as a mediator between the symptom cluster identified and physical activity behavior, instead of as an outcome,

as suggested by the TOUS. Functional limitation was found to be a significant mediator between the symptom cluster and physical activity behavior (Motl & McAuley, 2009).

While the TOUS has been used in a variety of clinical conditions, by far, the most studied phenomenon (both symptom and outcome) using the TOUS is fatigue. The psychological, physiological and situational antecedent factors of depression, breast feeding and disturbed sleep, respectively, all affected post-partum fatigue in military women (Rychnovsky, 2007). Post-partum fatigue was highly associated with the symptom of post-partum depression (Corwin, Brownstead, Barton, Heckard & Morin, 2005). Physiological factors of cigarette smoking and younger age, but not biological markers, (blood pressure, BMI, immune or inflammatory indices) were found to be correlated with fatigue (Corwin, Klein & Rickelman, 2002). Fatigue was a significant symptom in studies of cancer patients, patients with Chronic Obstructive Pulmonary Disease (COPD) and hemodialysis patients (Gift, Jablonski, Stommel & Given, 2004; Liu, 2006; Reishtein, 2004).

Few studies measured biomarkers as indicators of physiological antecedent factors. In their exploration of predictors of fatigue in healthy young adults, Corwin, Klein and Rickelman (2002) hypothesized that among other situational and psychological factors, physiologic antecedent factors including serum cotinine levels, (a metabolite of nicotine) and c-reactive protein and tumor-necrosis-alpha (inflammatory markers) would influence fatigue in a well population. While these biomarkers were not found to be significant predictors of fatigue in this population, the most important predictor was cigarette smoking. Corwin, Brownstead, Barton, Heckard and Morin (2005) included serum cortisol level, (a marker of stress), as a physiological predictor contributing to postpartum depression. While self-report of stress and fatigue were correlated with post-partum depression, serum cortisol was not. Moreover, serum cortisol levels

were not correlated with perceived stress (Corwin, Brownstead, Barton, Heckard & Morin 2005). McCann and Boore (2000) hypothesized that among other physiological factors, hemoglobin, hematocrit, ferritin, urea, creatinine, albumin, phosphate and calcium levels were associated with the symptom of fatigue. While they found a relationship between depression and fatigue, they were unable to demonstrate an association between the biological markers and fatigue (McCann & Boore, 2000).

Corwin, Klein and Rickelman (2002) introduced the concept of fixed and unfixed antecedent factors, a conceptual approach also included in Corwin, Brownstead, Barton, Heckard and Morin (2005). Fixed antecedent factors are those that cannot be changed, such as gender, age, family or personal history of depression and post-partum status. Because of its association with iron deficiency anemia, thyroid hormone deficiency and post-partum inflammatory status, fatigue was considered an unfixed physiologic factor in the post-partum depression study (Corwin, Brownstead, Barton, Heckard & Morin, 2005). BMI, resting blood pressure, inflammatory and immune status were considered unfixed physiologic factors in the study exploring predictors of fatigue in a well population (Corwin, Klein & Rickelman, 2002).

More studies utilizing the TOUS as an organizing framework and using performance as an outcome focused on the physical function aspect. For example, one study focused on the cognitive outcome of attentional function in women with breast cancer (Lee, 2005). Mood disturbance and symptoms each were associated with attentional function, and while symptoms were not found to mediate the relationship between mood disturbance and attentional function, symptoms did mediate the relationship between mood disturbance and attentional function when symptoms were rated at a medium level (not low or high) (Lee, 2005). Finally, Parks, Lenz, Milligan and Han (1999) introduced the notion that the impact of symptoms on performance

could actually extend outside the focal individual to affect others. They were able to demonstrate that infant development was higher when mothers were not persistently fatigued.

As expected, because of the concepts and relationships proposed in the TOUS, the nursing studies using the TOUS as a framework were focused on the nature of the relationships between antecedent factors, symptoms and outcomes. There were no studies testing nursing interventions using the TOUS. It is likely that the nature of these relationships in the clinical conditions studied has not been sufficiently explained yet to determine appropriate nursing interventions.

All but one study using the TOUS as the organizing framework were authored by nurses. However, the study examining the ability to predict future physical activity in patients with Multiple Sclerosis using symptoms was authored by kinesiologists (Motl & McAuley, 2009).

In summary, the TOUS has been used extensively to study the influence of symptoms and antecedent factors on outcome. Both physical performance and cognitive performance outcomes have been studied, as well as quality of life. Most propositions of the TOUS have been supported by research, with the most conflicting findings regarding the effect of antecedent factors on symptoms, which in turn affects function.

The TOUS has been modified several ways, sometimes limiting the focus to the impact of antecedent factors on symptoms. The TOUS has been used in a variety of clinical settings and conditions, with fatigue being the most studied symptom. While there is ambiguity regarding overlap of symptoms and antecedent factors, the theory is flexible and can be used in a variety of clinical situations. There is no specific inclusion of nursing intervention in the TOUS, although the implication is that identification of the salient antecedent factors and symptoms that affect outcome will lead to interventions designed to improve function (Lenz, Suppe, Gift, Pugh &

Milligan 1995). Interventions can target antecedent factors and symptoms. Since symptoms are conceptualized to be multiplicative, and all of the categories of concepts in the model (antecedent factors, symptoms and outcome) are proposed to be interactive, one intervention has the potential to affect more than one component of the model (Lenz, Pugh, Milligan, Gift & Suppe, 1997).

Biologic indicators of physiologic antecedent factors have been included in a few studies, and have not proved to have associations with the outcomes being studied. Biologic markers as an indicator of physiological antecedent factor deserve further study.

Use of the TOUS in This Study

The TOUS was selected as the framework for the current study because of the multiple antecedent factors found to contribute to the physical function outcomes for patients experiencing lumbar spinal degenerative problems (See Figure 1). The TOUS accurately depicts the reality that back pain and lumbar degenerative conditions are likely heterogeneous clinical conditions, the result of genetic, physiologic, behavioral and situational influences (Fourney, et al., 2011). The TOUS also allows for accurate depiction of the multiple symptoms experienced by individuals with lumbar degenerative conditions, and the many antecedent factors that likely contribute to the outcome of physical function in this population.

For the purposes of this research, physiological factors are defined as biologic and physical features possessed by the individual. Physiological factors influencing the symptom experience in this population are conceptualized to include genotype, body mass index (BMI), sex, age, and smoking. Situational factors are defined as features that are outside the individual that may influence health status and are conceptualized to include employment status, worker's compensation claim, and insurance type (commercial, Medicaid, Medicare, Tricare or none).

Psychological factors are defined as mental state or mood and are conceptualized to include depression. Physiological, situational and psychological factors are conceptualized to influence symptoms and physical function.

The physiological factors of BMI, sex, age and smoking have all been found to have independent and varying effects on back pain and physical function. Genotype is now associated with both the symptom of low back pain and lumbar disc degeneration. The psychological factor depression can influence the symptom of low back pain and physical function in individuals with lumbar degenerative conditions. The situational factors of litigation and worker's compensation influence physical function in individuals with lumbar degenerative conditions, and insurance type has been found to influence health outcomes in general. Finally, symptom research in this population is lacking and deserves further study.

Symptoms are defined as a perception of change in normal functioning in individuals (Lenz, Pugh, Milligan, Gift & Suppe, 1997). For the purposes of this study, symptoms will include the presence of back and/or leg pain, pain intensity (measured on a 10 cm visual analog scale) and associated symptoms of leg numbness and weakness. Symptom duration and distress will not be explored, but quality (numbness) of the sensory symptom will be included.

Physical function is the primary outcome variable for this inquiry. Physical function is defined as an individual's ability to perform in the various physical roles in their lives, to accomplish ADLS, to work, to carry out daily tasks for self and significant others, to be mobile and maintain leisure physical activities. Instruments used to measure physical function include the Oswestry Disability Index (ODI) and the physical functioning subscale of the SF-36.

For Aim 1, the contributions of patient physiological, situational and psychological factors to symptoms and to physical function will be explored, in order to demonstrate that

physical function in the population of persons with lumbar degenerative conditions is the result of a constellation of factors. For Aim 2, the combination of patient factors and symptoms will be explored to determine if profiles of specific variable combinations predict persons at greater risk for poorer physical function outcomes. For Aim 3, biologic data will be used to determine if genotype influences symptoms and physical function, or whether genotype, with other patient factors, can contribute to the ability to predict persons at risk for poorer physical function. Although patient factors are theorized to influence each other in the TOUS, these relationships are beyond the scope of this study.

In summary, the TOUS has been useful to guide inquiry into the influence of patient characteristics and symptoms in different clinical conditions. Several patient characteristics have been shown to influence many different outcomes for persons experiencing lumbar degenerative conditions. A few studies have explored the impact of back and/or leg pain on physical function in persons experiencing lumbar degenerative conditions. However, studies are lacking that explore the influence of patient characteristics and symptoms on the outcome of physical function in this clinical condition. In Chapter 3, Review of the Literature, each patient characteristic and symptom under study will be reviewed for their effects on physical function and other outcomes for persons experiencing lumbar degenerative conditions.

CHAPTER III

Review of the Literature

The review of literature will first address relevant lumbar spinal anatomy and the pathophysiological processes associated with degenerative changes that can lead to the symptoms of low back pain and leg pain and numbness. There are studies that explore the relationship between obesity, sex, smoking, *OPRM1* and *COMT* genotypes and physical function, and these will be reviewed in this chapter. While there are no studies that explore the relationship between the genes implicated in the structural integrity of the disc and physical function, it is known that disc degeneration can contribute to the development of the symptom of low back pain. This study will include all persons with lumbar degenerative conditions, in order to maintain the focus on symptoms and patient characteristics that may be common to all. In reality, many different lumbar degeneration diagnostic categories co-exist in the same individual.

The physiological, situational and psychological antecedent factors that have been shown to influence the symptoms and physical function will be reviewed. And, while many different genes have been identified to contribute to lumbar disc degeneration, only a few disc structural genes were included in this study. Genes involved in the degrading process of the disc have been identified, but these were not included in this study. Many genes have been implicated in the experience of pain. Only those encoding for *COMT* and *OPRM-1* are included in this study. Finally, the symptoms commonly experienced by individuals with lumbar degenerative conditions will be reviewed, along with the available literature regarding the effects of antecedent factors and symptoms on physical function.

Lumbar Spinal Anatomy and Degenerative Changes

The lumbar disc is situated between the vertebrae, and consists of a gelatinous inner core called the nucleus pulposis, encased by concentric layers of diagonally oriented collagen fibers called the annulus fibrosis. The nucleus contains proteoglycan molecules that hold water. The nucleus functions to absorb and accommodate compression loads. The annulus consists of type I and II collagen fibers, with cross-links of type IX collagen. The annulus holds the nucleus in place and attaches the disc to the vertebral bodies (Smith & Fazzalari, 2006).

Degenerative disc changes progress over time (Williams, et al. 2011). Ideally, there is a balance between synthesis and degradation of the constituents of the disc. Over time, however, the cells capable of synthesizing proteogylcans diminish in number, causing the water content of the nucleus to decline (Hadjipavlou, et al., 2008). This, in turn, causes the height of the disc to diminish. Cytokines, normally in balance with disc regeneration factors, gradually increase, contributing to degeneration (Hadjipavlou, et al., 2008). The disc structures become more disorganized, and the ability of the disc to resist normal forces is diminished. Conditions involving the intervertebral disc have been identified as a cause of low back pain (Cheung, Samartzis, Karppinen & Luk, 2012; Freemont, 2009; Livshits, et al, 2011; Takatalo et al., 2011). As degeneration progresses, the combination of facet joint arthritis and disc height reduction can produce changes that decrease the diameter of the canal and neuroforamen, which can contribute to spinal nerve symptoms of limb pain, numbness, tingling and weakness (Genevay & Atlas, 2010).

Lumbar disc degeneration and its accompanying symptoms are a multi-factorial health condition, likely resulting from both genetic and environmental factors. Evidence supporting the

key physiological, situational, and psychological variables to be examined in this study are summarized according to the TOUS model.

Physiological Factors

Several physiological variables influence symptoms associated with lumbar disc degeneration. There is some evidence linking these physiological variables with physical function in persons with lumbar degeneration. The physiological variables to be examined in this study include body mass index (BMI), sex, age, smoking status and genotype, each discussed in detail here.

Obesity

Obesity is a patient characteristic that is a strong risk factor for low back pain (Heuch, Hagen, Heuch, Nygaard & Zwart, 2010; Heuch, Heuch, Hagen & Zwart, 2012; Shiri, Karppinen, Leino-Arjas, Solovieva & Viikari-Juntura, 2010; Shiri, et al., 2008). BMI greater than 30 is a risk factor for the development of low back pain in persons without baseline low back pain, even when adjusted for age, work status, education, physical activity and smoking (Heuch, Heuch, Hagen & Zwart, 2013).

Persons with overweight or obese BMI values are more likely to have disc degeneration and more likely to have greater severity of disc degeneration at more levels (Samartzis, Karppinen, Chan, Luk & Cheung, 2012). Being overweight at any age increases the risk of lumbar disc degeneration, but persons who are overweight at an earlier age have a greater risk of lumbar disc degeneration (Liuke, et al., 2005). Takatalo et al. (2013) demonstrated that higher adiposity measures, including waist circumference and body fat percentage were associated with lumbar disc degeneration in males, but not in females. In a study of Japanese persons over the age of 50, the odds ratio of having lumbar disc degeneration was greater at nearly every lumbar

level for those with BMI greater than or equal to 25 (Hangai et al., 2008). Specifically, the odds ratio was 2.98 (95% CI 1.52-6.05), 3.58 (95% CI 1.85-7.21), 2.32 (95% CI 1.18-4.72), and 3.34 (95% CI 1.70-6.81) for L2-3, L3-4, L4-5 and L5-S1 levels, respectively (Hangai et al, 2008). In obese individuals, physical function outcomes have been worse for operative and non-operative treatment for lumbar disc herniation (Rihn, et al., 2013).

In summary, in persons who are obese, there is a higher risk of disc degeneration, one cause of low back pain. Moreover, in those obese at a younger age, there is a greater risk of disc degeneration at more levels. Obesity is also directly associated with low back pain.

Sex and Age

While the experience of pain varies between females and males, it is not clear whether lumbar disc degeneration differs in rate and severity between females and males. One systematic review suggested that the rate of progression of lumbar disc degeneration was greater in females ages 50-59; with disc degeneration in males progressing faster during ages 60-79 (Lee, Dettori, Standaert, Brodt & Chapman, 2012). However, a cadaveric study failed to show any difference in disc degeneration rates between females and males (Siemionow, An, Masuda, Andersson & Cs-Szabo, 2011).

Females may experience greater pain levels and worse physical function than males with lumbar stenosis. Kim et al. (2013) identified significantly worse pain VAS and ODI scores for women than for men, even after controlling for BMI, age, and severity of disc degeneration and stenosis.

The prevalence of disc degeneration does increase with age (Cheung, et al., 2009). The prevalence of disc degeneration is estimated to be as high as 40% for individuals under the age

of 30 (Cheung, et al., 2009). By age 50, the prevalence rises to 60-90% (Cheung, et al, 2009; Kalichman, Kim, Li, Guermazi & Hunter, 2010).

In summary, it is not clear whether the rate and prevalence of disc degeneration varies by sex. Sex differences in estimations of pain in lumbar stenosis have been identified. Disc degeneration increases with age.

Smoking

Smokers have a higher incidence of back pain than non-smokers (Karahan, Kav, Abbasoglu & Dogan, 2009; Shiri, Karppinen, Lein-Arjas, Solovieva, & Viikari-Juntura, 2010). Current smokers had the highest risk of low back pain, compared with former and never smokers in one meta-analysis (Shiri, Karppinen, Leino-Arjas, Solovieva & Viikari-Juntura, 2010). Specifically, the odds ratio for low back pain in current smokers in the past month was 1.30 (95% CI 1.16-1.45), for low back pain in the past 12 months, 1.33 (95% CI 1.26-1.41), for seeking care for low back pain,1.49 (95% CI 1.38-1.60, for chronic low back pain, 1.79 (95% CI 1.27-2.50), and for disabling low back pain, 2.14 (95% CI 1.11-4.13) (Shiri, Karppinen, Leino-Arjas, Solovieva, S. & Viikari-Juntura, 2010). Data from the Nurses' Health Study reveal that current smokers have a higher risk of lumbar disc herniation than former and never smokers, and the risk increases with number of cigarettes smoked per day (Jhawar, Fuchs, Colditz & Stampfer, 2006). Among patients presenting for treatment for spine complaints, current smokers had highest baseline Oswestry Disability Index (ODI) scores (a lumbar disease-specific instrument to measure function), followed by former then never smokers (44.22, 38.11. 36.02, respectively) (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012). Current smokers in treatment for spine-related pain had higher pain visual analog scores (VAS) than nonsmokers, and those

smokers who quit during treatment experienced greater improvement in VAS pain scores (Behrend, Prasarn, Coyne, Horodyski, Wright & Rechtine, 2012).

Along with aortic calcification and stenosis of the lumbar arteries, high cholesterol levels and smoking were associated with low back pain and lumbar disc degeneration in a systematic review (Kauppila, 2009). The relative risk for smokers compared to non-smokers to be hospitalized for a lumbar disc degeneration-related cause in a Swedish prospective cohort study was 1.27 (95% CI 1.15-1.39) (Wahlstrom, Burstrom, Nilsson & Jarvholm, 2012). Smokers had 18% greater mean lumbar disc degeneration scores than non-smokers (Battie et al., 1991).

Genotype

Lumbar disc degeneration has traditionally been considered to be the result of age, sex, occupation, smoking and repetitive vibration. More recently, however, hereditary and biological mechanisms contributing to disc degeneration have been identified (Zhang, Sun, Liu & Guo, 2008). Scientists have discovered several genes that contribute to disc degeneration and to disc structural integrity. Lumbar disc degeneration is now considered to be a complex process with both genetic and environmental contributors (Hadjipavlou, Tzermiadianos, Bogduk & Zindrick, 2008).

Selected Candidate Genes for Disc Structure

Genes that are associated with the structural components of the disc that help to maintain its integrity include those that code for collagen (*COL9A2* and *COL9A3*, with others), *aggrecan* (*ACAN*), and vitamin D receptors (*VDR*) (Hadjipavlou, et al., 2008; Kao, Chan, Samartzis, Sham & Song, 2011).

Collagen IX Alpha 2 and Alpha 3 (COL9A2 and *COL9A3) Genes*

The intervertebral disc contains an extracellular matrix of proteoglycans and collagen. The inner portion of the disc, the nucleus pulposis, consists mainly of proteoglycans (about 50%) with about 20% collagen II (Annunen, et al., 1999). Both the proteoglycan and the collagen II contain small amounts of collagen IX. Collagen IX contains three genetically distinct chains, alpha 1, alpha 2, and alpha 3 (Diab, Wu & Eyre, 1996). Collagen IX is believed to function as a link between collagens and non-collagenous proteins in tissues (Annunen, et al., 1999). These cross links are believed to play an important role in protecting the disc from distension from aggrecan and water by their interconnected network, thereby absorbing and distributing loads (Aladin, et al., 2007; Diab, Wu & Eyre, 1996). The Collagen Type IX, Alpha-2 (*COL 9A2*) gene codes for the alpha 2 chain and the collagen Type IX, Alpha-3 (*COL9A3*) codes for the alpha 3 chain (Kalichman & Hunter, 2008).

Polymorphisms in the *COL9A2* and *COL9A3* genes (location 1p34.2 and 20q13.33, respectively) have been implicated in changes of the type IX collagen that make it more unstable, making the disc more susceptible to mechanical stress (Hadjipavlou, Tzermiadianos, Bogduk & Zindrick, 2008). An arginine (wild-type) to tryptophan (*Trp3*) change in the *COL9A3* gene has been associated with a higher risk of disc degeneration among obese individuals (Solovieva, et al., 2002). A glutamine to tryptophan (*Trp2*) change in the *COL9A2* gene has been associated with disc degeneration (Annunen, et al., 1999; Jim, et al., 2005; Rathod, et al., 2012).

Results from a Japanese study of 84 patients who underwent surgery for herniated disc seemed to suggest that those possessing the *Trp2* allele were more likely to have developed disc degeneration at an earlier age (Higashino et al, 2007). The *Trp3* allele was not identified in this Japanese population. Although there was no statistically significant association between the

Trp2 allele and disc degeneration for those over 40 years of age, the authors found that for those under the age of 40, there was a six-fold greater chance of having disc degeneration for those possessing the *Trp2* allele (Higashino et al., 2007). Conflicting findings in a large (N=470 cases and 658 controls) Japanese population were published by Seki et al. (2006). The *Trp2* allele was actually under-represented in those with lumbar intervertebral disc degeneration. Instead, the authors found that a specific haplotype was over-represented in those with lumbar intervertebral disc degeneration (Seki, et al., 2006).

The finding of polymorphisms of the *COL9A2* and *COL9A3* genes influencing the development of disc degeneration is not consistent among different ethnic groups, however. This is due in part to the frequency with which the *Trp2* and *Trp3* alleles are found in different ethnic populations. Several genetic association studies have investigated the role of the *COL9A2* and *COL9A3* genes in disc degeneration, including Finnish, (Annunen et al., 1999) Japanese, (Higashino, 2007; Seki, et al., 2006) southern Chinese (Jim et al., 2005) and Indian (Rathod et al., 2012).

In summary, both *COL9A2* and *COL9A3* play a role in the integrity of the intervertebral disc. Certain polymorphisms have been associated with more degenerative changes within the disc, although their representation varies among ethnic groups.

Aggrecan (ACAN) Gene

Aggrecan is a large chondroitin sulfate proteogycan that functions to hold water content within the disc, making it more resilient to compressive and mechanical forces (Solovieva et al, 2007; Watanabe, Yamada & Kimata, 1998). With age, the proteoglycan content of the disc diminishes, and the disc becomes thinner and more fibrotic, resulting in the disorganization of the disc components (Modic & Ross, 2007).

Variable numbers of tandem repeat (VNTR) polymorphisms in the aggrecan (*ACAN*) gene, located on chromosome 15q26, have been linked to different levels of lumbar disc degeneration. The variable number of tandem repeats results in different length aggrecan proteins possessing differing numbers of attachment sites for chondroitin sulfate. Shorter alleles have been found to be associated with greater degrees of disc degeneration and development of disc degeneration at an earlier age (Eser, et al., 2010; Kawaguchi, et al., 1999). However, these results have not been consistently replicated. For example, one study found that individuals homozygous for 26 VNTRs experience a higher risk of lumbar disc degeneration and that 25 and 28 VNTRs may actually be protective (Solovieva, et al., 2007).

In summary, *ACAN* plays a role in disc integrity by its ability to attach proteoglycan molecules, keeping the disc hydrated. Findings thus far suggest that greater variable numbers of tandem repeats that encode for longer *ACAN* molecules provide for more proteoglycan attachment sites, and may be protective for the disc.

Vitamin D Receptor (VDR) Gene

Vitamin D receptor gene (*VDR*) is associated with osteoporosis and osteoarthritis (Kalichman & Hunter, 2008; Kawaguchi, et al., 2002). The exact influence *VDR* variants have on intervertebral disc degeneration is not known, but may play a role in the structure of cartilage cells (Balmain, Hauchecorn, Pike, Cuisiner-Gleizes & Mathieu 1993; Yuan, et al., 2010). The location of vitamin D receptor gene is near to the genes for insulin-like growth factor and type II collagen, and may be a marker for other genes that influence disc degeneration (Kawaguchi et al., 2002; Kalichman & Hunter 2008).

Single nucleotide polymorphisms of the *VDR* gene (location 12q13.11) have been associated with higher incidence of lumbar disc degeneration. In *TaqI* and *FokI* polymorphisms

tt, *Ff*, and *ff* genotypes have been found to be associated with more severe grades of disc degeneration (Eser, et al. 2010; Videman et al., 1998). Yuan, et al. (2010) was unable to demonstrate the *VDR TaqI tt* genotype in a population of Chinese individuals, but there was a significant increased risk for disc degeneration in persons with the *VDR-apa aa* genotype.

In summary, many candidate genes have been studied for their effect on lumbar intervertebral disc degeneration. There is a beginning understanding of the influence of many genes on disc degeneration, but the mechanism and degree of contribution of each candidate gene has not been well established to date. The studies on the candidate genes and their effect on intervertebral disc degeneration differ in methodology, making it difficult to compare findings across studies. The methods for determination of degree of disc degeneration also vary between studies. It is becoming clear that findings differ across ethnic groups. More studies must be undertaken before clarity in the genetic contribution to intervertebral disc degeneration is achieved.

Selected Candidate Genes for Pain

While many genes have been associated with increased susceptibility to pain, the pain genotype variables included for this study are opioid receptor mu-1 and catechol-O-methyltransferase (*OPRM-1* and *COMT*).

Opioid Receptor, mu-1 (*OPRM1*) Gene

Opioid receptor sites play a role in pain. Genetic differences in opioid receptor sites have been found to play a role in the experience of pain. Differences in *mu-opioid* receptors influence pain perception and post-operative analgesic requirements in many studies (Chou, et al., 2006; DeCapraris, et al., 2011; Henker, et al., 2012; Tan, et al., 2009). The receptors are activated by both endogenous opioids and opioid drugs (Mura et al., 2013).

The SNP A118G allele has been widely studied, with conflicting findings regarding pain thresholds and opioid requirements for various pain states. The A118G allele is expressed differently in ethnic subgroups.

There is evidence that the A118G allele is associated with increased opioid requirements in various pain states, including post-operative, migraine and cancer pain (Chou, et al., 2006; Gong, et al., 2013; Menon, et al., 2012; Sia, et al., 2013). There is also evidence that pain threshold may be higher in persons with the A118G *OPRM1* allele, although one study was able to validate this finding only for Caucasians (Hastie et al., 2012; Huang, et al., 2008). However, the A118G allele has also been associated with higher pain ratings in women, and had no effect on cortical pain processing in individuals with chronic back pain compared to healthy controls (Fillingim, et al., 2005; Vossen, Kenis, Rutten, van Os, Hermens & Lousberg, 2010).

In persons with lumbar disc herniation, pain levels during the subsequent year varied by sex and *OPRM-1* genetic differences, irrespective of treatment type (operative and non-operative) (Olsen, et al., 2012). The single nucleotide polymorphism (SNP) A118G was associated with less pain in men, but was associated with slower recovery and greater pain levels in women, in both operative and non-operative treatment groups. One meta-analysis failed to validate differences in pain level and analgesic requirements based on variation in *OPRM-1* genotype (Walter & Lotsch, 2009).

In summary, there is evidence for increased pain threshold and increased opioid requirements in persons with the A118G allele, but these findings have not been consistent, and some studies have failed to demonstrate the A118G allele affects cortical pain processing, pain threshold, or opioid requirements.

Catechol-o-Methyltransferase (*COMT*) *Gene*

Catechol-o-methyltransferase (*COMT*) is involved in the metabolism of neurotransmitters, inactivating catecholamines. *COMT* may have an influence in the function of mu-opioid receptors, which are regulated by neurotransmitters (Zubieta, et al., 2003). Zubieta et al., (2003) studied opioid receptor site activity and pain responses in a small sample of individuals to determine if different polymorphisms were associated with different levels of opioid receptor site activation and different pain levels. They were able to demonstrate that individuals homozygous for the *met/met* allele in the *COMT* gene demonstrated lower *μ-opioid* system responses and had higher reported levels of pain (Zubieta et al., 2003). The volume of hypertonic saline necessary to reach a preset level of pain intensity was also lower in *met/met* individuals. Individuals with high *COMT* activity (*val/val*) had higher mu-opioid system activation. *COMT* genotype is associated with processing of pain in the brain, demonstrated by Positron-Emission Tomography (PET) scanning in the Zubieta et al (2003) study and by functional Magnetic Resonance Imaging (MRI) (Schmahl, et al., 2012).

Specific *COMT* polymorphisms have been associated with increased pain perception and the development of chronic pain states (Diatchenko et al., 2005; Henker et al., 2012; Orrey et al., 2012;). The studies involving *COMT* have focused on haplotypes and single-nucleotide polymorhpisms. Diatchenko et al. (2005) demonstrated that nearly 11% of the variability in sensitivity to experimental pain in females could be attributed to three distinct *COMT* haplotypes based upon genotype at four SNPs. Persons with haplotype GCGG had the lowest responsiveness to experimental pain, designated as the low pain sensitivity (LPS) haplotype. Individuals with haplotype ATCA had intermediate pain responsiveness, designated as APS haplotype. The

greatest pain responsiveness was observed in individuals heterozygous for ATCA and ACCG haplotypes, designated the high pain sensitivity (HPS) haplotype.

Single-nucleotide polymorphisms variants of *COMT* have been studied, with mixed results. Studies investigating the outcomes of surgical and non-surgical treatment for low back pain suggest that *COMT* polymorphism plays a role in pain levels and outcome, although sample sizes were small, and study methods differed (Dai, et al., 2010; Omair, Lie, Reikeras, Holden & Brox, 2012). By far the most studied is the *Val*158*Met* variant. *Val* 158 homozygous individuals have increased *COMT* activity compared to *Met* homozygous individuals, with heterozygotes possessing intermediate activity (Dai et al., 2010; Lotta et al., 1995; Lachman et al., 1996).

COMT activity in general has shown an inverse correlation with pain sensitivity (Dai, et al., 2010). However, studies examining the association of the *Val*158*Met* SNP with pain and functional outcomes have produced mixed results. Omair et al., (2012) found *Val*158*Met* heterozygotes with discogenic low back pain randomized to surgical and non-surgical treatment experienced a greater pain improvement after treatment than either *Met* or *Val* homozygotes, although the effect was small. In contrast, no significant association was found between the *Val*158*Met* polymorphism and improvement in post-operative ODI scores in a population of individuals after lumbar fusion surgery for discogenic pain (Dai et al., 2010).

In summary, while the effects of *COMT* are known with regard to the effects on neurotransmitters, its effects on the experience of pain remain unclear. While some associations between *COMT* SNPs and haplotypes and the experience of pain have been observed, the findings have been inconsistent. Moreover, the studies have varied widely in method, population, and outcome measures used. Overall, the observed associations of both *OPRM1* and *COMT* genotypes and pain are small, supporting the notion that prediction of treatment outcome

in persons with lumbar degenerative conditions is likely related to a constellation of patient characteristics. There is some evidence that links *OPRM1* and *COMT* genotypes to the symptom of pain and to physical function in populations with lumbar degenerative conditions.

In summary, many physiological factors have been associated with lumbar degenerative conditions and the symptoms associated with lumbar degenerative conditions. It is hypothesized that genotype, BMI, sex, age and smoking physiological factors have the potential to interact with symptoms to affect physical function in individuals with lumbar degenerative conditions. Certain situational factors may also interact with symptoms to affect physical function in individuals with lumbar degenerative conditions.

Situational Factors

Evidence suggests that patient situational factors influence the outcome of lumbar degenerative conditions. The situational variables included for this study are employment status, worker's compensation claim, and insurance type.

Employment Status

Being unemployed has a negative impact on post-treatment outcomes for persons undergoing treatment for lumbar degenerative conditions. Those working pre-operatively were ten times more likely to be working post-operatively after lumbar fusion surgery (Anderson, Schwaegler, Cizek & Leverson, 2006; Burnham et al., 1996; Silverplats et al., 2010; Zieger, et al., 2011). For patients undergoing lumbar surgery, length of time off work preoperatively was a strong predictor of outcome in visual analog pain scores and function as measured by the ODI. Patients off work for 13 weeks or less had more favorable outcomes for pain and physical function than those who were off work for longer than 13 weeks, regardless of the surgical procedure (Rohan et al., 2009). While the exact reason for this observation is not known, in

general, the longer an individual is off work related to a spine cause, the less likely that individual is to return to work, and employment prior to surgical treatment was associated with better physical function and less pain postoperatively (Guyer, et al., 2008; Nguyen, Randolph, Talmage, Succup, & Travis, 2011).

Similar findings were reported for patients receiving intensive non-surgical treatment for chronic low back pain. Out of all patient characteristics studied, working prior to treatment was the variable most strongly associated with improved physical function scores on the ODI after treatment (van Hooff, Spruitt, O'Dowd, van Lankveld, Fairbank & van Limbeek, 2013). In summary, being employed prior to treatment for lumbar degenerative conditions and associated low back pain is associated with better physical function after treatment.

Workers Compensation

Patients receiving worker's compensation had worse functional status after surgical and non-surgical treatments for spine conditions (Anderson, Subach, & Riew, 2009; Atlas, Chang, Kamman, Keller, Deyo, & Singer, 2000; Burnham, et al, 1996; Voorhies, Jiang & Thomas, 2007; Yang, Lowe, de la Harpe & Richardson, 2010). In one meta-analysis of worker's compensation and outcome after any surgical procedure, patients receiving worker's compensation had worse outcomes after surgery measured by a disease-specific outcome instrument, a general functional score, a general health outcome score, a patient satisfaction score or a pain score (Harris, Mulford, Solomon, van Gelder & Young, 2005). The summary odds ratio for an unsatisfactory outcome after surgery in persons receiving worker's compensation was 3.79 (95% CI 3.28-4.37) (Harris, Mulford, Solomon, van Gelder & Young, 2005).

Similarly, patients receiving worker's compensation after a low back injury were less likely to return to work than those not receiving worker's compensation (Crook, Milner, Schultz

& Stringer, 2002). Worker's compensation and litigation are both associated with worse ODI scores in patients presenting for treatment for complaints of spine and/or limb pain (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012).

Insurance Type

Insurance type can be associated with less optimal health outcomes. Patients with indigent care plans tend to have reduced access to standard of care and less optimal treatment outcomes across a variety of health conditions (Greenstein, Moskowitz, Gelijns & Egorova, 2012; Kruper, et al., 2011; McClelland, Guo & Okuyemi, 2011; Yorio, Yan, Xie & Gerber, 2012). Over a several year period, uninsured patients had more complications and longer intensive care stays after neurosurgery than Medicaid patients, and Medicaid patients had more complications and longer intensive care stays than Medicare patients in a major Midwestern medical center (El-sayed et al. 2012). However, in Nationwide Inpatient Sample, outcomes after surgery for spinal metastasis did not differ among uninsured, Medicaid, or Medicare patients, after adjusting for acuity of presentation (Dasenbrock et al., 2012).

A medline search revealed no studies examining the relationship of insurance type with low back pain, lumbar degenerative conditions, or physical function in this population. However, insurance plans differ substantially in the type and extent of covered treatments. Many health plans restrict access to diagnostic imaging and treatments, including physical therapy and spinal injections. Lack of access to these interventions may influence symptom control and physical function in persons with lumbar degenerative conditions.

In summary, being off work and having a worker's compensation claim have been associated with worse outcomes for individuals experiencing lumbar degenerative conditions.

While no studies addressed the influence of insurance type on outcomes for individuals with lumbar degenerative conditions, insurance type can affect outcomes of health care in general.

Psychological Factors

Psychological factors also play an important role in the outcome of treatment for many spinal conditions. The psychological variable included for this study is depression.

Depression

Depression can contribute to the development of chronic low back pain and is negatively correlated with outcome and return to work after surgery for lumbar herniated disc (Carragee, Alamin, Miller & Carragee, 2005; Kohlboeck et al, 2004; Pincus, Burton, Vogel & Field, 2002; Trief, Grant & Fredrickson, 2000). In an asymptomatic cohort of veterans, depression was a more reliable predictor of future back pain episodes than baseline MRI findings (Jarvik, Hollingworth, Heagerty, Haynor, Boyko, & Deyo, 2005). Depressed patients have worse functional scores and higher pain visual analog ratings than non-depressed patients with similar musculoskeletal conditions (George, et al., 2011; Kaptan, Yelcin & Kasimcan, 2012).

In summary, physiological, situational and psychological factors have been shown to significantly influence the outcome of treatment for lumbar degenerative conditions. However, studies assessing the combined effect of multiple physiological, situational and psychological factors on the outcome of treatment for lumbar degenerative conditions are lacking. Recognizing that outcomes for this population are likely due to a multifactorial process, there is a need for more research addressing the combined effect of these factors.

Symptoms in Persons with Lumbar Degeneration

Symptoms are subjective phenomena that indicate a change in health or normal function (Dodd, et al., 2001; Fu, LeMone, & McDaniel, 2004; Farrar, Berlin, & Strom, 2003; Fu,

McDaniel, & Rhodes, 2007). Fu, McDaniel and Rhodes (2007), define symptom occurrence as the frequency the symptom is experienced over a period of time, and symptom distress as the discomfort or suffering accompanying the symptom. Symptoms possess the dimension of timing, frequency, intensity, duration, and meaning, (Armstrong, 2003). In general, the worse the symptom experience, the more negative the impact on outcome.

Symptoms of lumbar degenerative conditions include low back pain and limb numbness, pain, and weakness. Narrowing of the central spinal canal (stenosis) from ligamentum flavum hypertrophy, bone spurs, and bulging of the outer annulus can contribute to neurogenic claudication, which refers to lower limb symptoms of pain, weakness, sensory alteration and fatigue (Genevay & Atlas, 2010). Stenosis of the lateral aspects of the spinal canal or the neuroforamen can cause radicular symptoms, which refers to leg pain and sensory alteration that corresponds to the particular nerve root affected, with weakness in the corresponding myotome (Genevay & Atlas, 2010). Since the lumbar facet joints and the posterior annulus of the intervertebral disc are enervated, degenerative changes in these structures can contribute to low back pain (Falco et al., 2012; Moon et al., 2012; Van Zundert, Vanelderen, Kessels & van Kleef, 2012).

The intensity of symptoms has been associated with worse outcomes. Greater pain and anxiety after discharge for severe burn injuries predicted increased fatigue, increased pain, and decreased physical function; even at the two-year follow up (Edward, et al., 2007). Wilson, Robinson, and Turk (2009) clustered fibromyalgia symptoms based on physical or cognitive/psychological categories, and low, moderate, or high intensity. Subjects with the more intense symptoms in both the physical and cognitive/psychological categories used more health care resources, had the worst physical function, and least favorable work characteristics.

There is limited literature examining the relationship of symptoms to outcome in persons with degenerative lumbar spinal conditions, although persons with both back and leg pain tend to do worse than persons with back pain alone, across many outcome measures. Symptom location in both the back and leg and greater symptom intensity predicted greater disability in lumbar spinal stenosis patients (Lin, Lin, & Huang, 2006). Individuals experiencing both leg and back pain experienced greater pain irritability and activity limitation and missed more work than individuals with back pain alone in a large Danish study of over 2,600 patients (Kongstead, Kent, Albert, Jensen & Manniche, 2012). Persons defining their pre-operative pain with more intense adjectives from the McGill Sensory and Affective Scores experienced worse outcomes after surgery for herniated disc (Voorhies, Jiang & Thomas, 2007).

Physical Function

Physical Function is a concept often used in health care, yet its definition remains unclear and its use is inconsistent (Leidy, 1994). Often, the meaning of physical function is implied. Sometimes used interchangeably with quality of life, functional status, and health status, it has been measured by many different methods. Physical function has conceptually been used as a predictor, mediator, and outcome. Optimization of physical function is a key focus for health care professionals, and it is a requisite part of overall quality of life (Rejeski & Mihalko, 2001, Ferrans, et al., 2005). Physical function has been described as foundational to the ability to operationalize roles (Lenz, et al, 1997). Physical function forms the basis for an individual's ability to accomplish the activity required to provide for basic needs, fulfill life roles, and maintain health and well-being (Hoffman, et al., 2009). In their update to the TOUS, Lenz, Pugh, Milligan, Gift and Suppe (1997) conceptualize the functional performance outcome of the model to include physical activity, activities of daily living, social activities, and role

performance (which includes work). In this study, physical function is operationally defined by the use of the ODI and the physical function subscale of the SF-36. An important distinction should be noted between physical function as measured by a disease-specific lumbar instrument and the physical function subscale of the SF- 36. Physical function as measured by the ODI may represent a portion of global physical function of an individual. The ODI represents the portion of physical function that may attributable to lumbar spine influences.

The World Health Organization (WHO, 2002) has defined disability as consisting of "impairments, activity limitations and participation restrictions". Human functioning is divided into three levels: the individual body part, the whole person, and the person in a social context (WHO, 2002). Activity is one component of functioning according to the WHO, and is defined as "the execution of a task or action by an individual". Participation is another component of functioning. Participation "is involvement in a life situation" (WHO, 2002). The WHO also describes environmental factors that impact functioning, similar to the physiological, situational and psychological antecedent factors in the TOUS. These include the "physical, social and attitudinal environment in which people live and conduct their lives" (WHO, 2002). For this study, physical function is defined as an individual's ability to fully perform in the various physical roles in their lives, to accomplish ADLS, to work, carry out daily tasks for self and significant others, to be mobile, and maintain leisure physical activities.

Low back pain symptom aggravation by movement is associated with worse ODI scores (Cai, Pua & Lim, 2007). Low back pain has a negative effect on physical activity and was associated with measures of disability in a Turkish population (Soysal, Kara & Arda, 2012). Physical function is worse for individuals with low back pain accompanied by leg pain than for those individuals with back pain alone (Kongsted, Kent, Albert, Jensen & Manniche, 2012;

Konstantinou, et al., 2013; Prins, van der Wurff & Groen, 2013). Individuals rating their back and leg pain as equal experienced greater interference with physical function as measured by ODI scores than those rating back pain or leg pain as greater (Sigmundsson, Jonsson & Stromqvist, 2013). Hirano et al., (2014) found that back pain and knee pain had stronger associations with reduced physical function in an elderly population than leg pain or leg numbness. In a cohort of individuals with lumbar spinal stenosis, back and leg pain severity as measured by VAS was negatively associated with physical function scores on the ODI, even when adjusted for age and degree of canal stenosis (Kim, et al., 2013). Pain sensitivity, measured by the Pain Sensitivity Questionnaire, was associated with the severity of pain measured by the VAS (Kim, et al., 2013). Kongsted, Kent, Albert, Jensen and Manniche (2012) also found that individuals with back and leg pain with signs of nerve root irritation (depressed reflexes, weakness, sensory alteration and positive neurotension signs) had worse estimations of pain and physical function than individuals with back pain alone and individuals with back pain and leg pain without signs of nerve root irritation.

In summary, multiple patient factors have been found to independently influence outcomes, including physical function, for persons experiencing lumbar degenerative conditions. These factors include physiological, situational, and psychological variables and symptoms. Many of these patient factors have been studied separately for their influence on outcomes in individuals experiencing lumbar degenerative conditions. More symptom research in this population is needed. While there are studies examining the relationships between certain genotypes and their influence on disc degeneration, pain, and functional outcomes in persons with lumbar degenerative conditions, there are no studies that attempt to identify a profile of these combined factors and their influence on physical function. A gap of knowledge exists

related to how these patient factors and symptoms interact to affect physical function for persons with degenerative lumbar spinal conditions. Therefore, the aims of this study will address these factors, symptoms, and genotype to begin to identify their combined effects on physical function in a population of adults experiencing lumbar degenerative conditions.

CHAPTER IV

Methods

Research Design

A cross-sectional, descriptive study design was employed to address the proposed aims. A randomized sample consisting of individuals referred to a tertiary spine service outpatient clinic at multi-specialty neuroscience center was used. The following Aims were used to guide the study. Aim 1 focused on determining the contribution of physiological (BMI, sex, age, smoking status), situational (employment status, worker's compensation claim, insurance type), and psychological (depression) characteristics in persons receiving non-surgical interventions for degenerative lumbar conditions to symptoms and physical function. Aim 2 sought to develop a predictive model for the outcome of physical function in persons receiving non-surgical interventions for lumbar degenerative conditions, using symptoms (back and/or leg pain, numbness and weakness) and physiological, situational, and psychological patient characteristics. The exploratory aim was to examine the impact of the physiological characteristic genotype (disc structural genes and pain genes) on symptoms (back and/or leg pain, numbness, and weakness) and on physical function in persons experiencing lumbar degenerative conditions.

Subjects for Aims 1 and 2 were randomly chosen from a database of approximately 1,300 individuals with completed baseline ODI and SF-36 instruments from the tertiary spine service outpatient clinic from 2009-2012. Patients are referred to the tertiary spine service from primary care providers and other specialty providers. The spine center is a regional source for specialty spine care, treating patients for degenerative and trauma-related spine problems. For Aim 3, a

randomly selected subset of the study sample for Aims 1 and 2 was used to explore the impact of genotype on symptoms and physical function.

Sample.

The study sample consisted of persons referred to the spine service at the Hauenstein Neuroscience Center at Mercy Health Saint Mary's from February 2009 through early 2012, with symptoms of back and/or leg pain. As part of the intake process, every patient with a new encounter at the spine service completed SF-36 and ODI questionnaires, placed in the patient chart as part of the medical record. All of the raw scores from the completed SF-36 and ODI questionnaires were also entered into a separate excel data sheet and contained in a password protected computer file on the hospital system hard drive. The spine service at the Hauenstein Neuroscience Center has a data base that includes completed baseline ODI and SF-36 questionnaire responses from approximately 1,300 patients. This password protected file is stored on the hospital hard drive, under the heading "Groups". A computer program for random numbers was applied to the excel sheet containing patients with completed ODI and SF-36 questionnaires to arrange individuals in a random order. Medical records were reviewed proceeding from the beginning of this randomly arranged list, until an adequate sample of individuals with completed questionnaires and complete physiological, situational and psychological data were identified.

Inclusion criteria were: 1) aged 18 years or older, 2) back and/or leg complaints of pain, numbness, and/or weakness, 3) completed SF-36 and ODI information at first clinic visit, 4) complete information on selected patient factors and symptoms, including a completed anatomic pain drawing, 5) English-speaking. All eligible persons with lumbar degenerative conditions were included. Exclusion criteria were: 1) spinal cancer (primary or metastatic), 2) myelopathy

or cauda equina syndrome, 3) major psychiatric disorder (personality disorder, schizophrenia and bipolar illness), 4) spinal fracture, 5) spinal infection, 6) being scheduled for surgery, 7) pain in the neck and upper extremities, 8) lumbar surgery within the last year, and 9) current pregnancy. Prisoners, considered a vulnerable population in research, were not treated in the outpatient spine service.

The target sample size for Aims 1 and 2 was 154. This determination was based on Tabachnick and Fidell's (2006) recommendations for sample size using multiple regression. Tabachnik and Fidell recommend 8(k) + 50 as a general rule for multiple regression, with k = number of independent variables. Considering BMI, sex, age, smoking status, employment status, workers compensation claim, insurance type, depression, pain visual analog score, back pain, leg pain, numbness and weakness as separate independent variables, as in Aim 2, the required sample size was 154.

All but the genotype data were obtained from the medical record. The raw scores for SF-36 and ODI questionnaires were obtained from the separate excel data sheet from the password protected file on the hospital hard drive. A randomly selected subset of the study participants with completed ODI and SF-36 questionnaires and complete physiological, situational and psychological data were contacted regarding genotyping. Aim 3 subjects were selected by applying a computer program for randomization to the excel sheet containing the patients with completed ODI and SF-36 questionnaires and all physiological, situational and psychological data, to arrange these individuals in a random order. Working from the top of this list, Aim 3 subjects were contacted sequentially by phone to participate in genotyping. Since Aim 3 is exploratory, a smaller sample size of 30 subjects was used as a target. Since the subjects for Aim

3 were randomly selected from the study sample for Aims 1 and 2, identical eligibility criteria were used.

Setting.

The spine service is located in the Hauenstein Neuroscience Center at Mercy Health Saint Mary's, a 343-bed urban teaching hospital in Grand Rapids, Michigan. Persons with spinal symptoms are referred to the outpatient spine service by primary care providers and other specialists. These providers are mainly from Kent County, Michigan, but also include those from several outlying counties. There were more than 4,000 patient visits to the spine service in fiscal year 2011. The providers in the spine service are a contracted physiatrist and an employed nurse practitioner. The providers work collaboratively with on-site contracted neurosurgeons, independent provider pain specialists and employed physical therapists specially trained in the management of spinal disorders. Mercy Health Saint Mary's is part of a larger Catholic health system, Trinity Health. Because of the Catholic mission of Mercy Health Saint Mary's and Trinity Health, the spine service provides care to the uninsured and underinsured. Complete ODI and SF-36 intake data are available for more than 1,300 patients currently in the spine service database.

Instruments and Measures.

All data for the proposed research were extracted from the medical record, except for genotype data. The specific instruments used to measure each variable are discussed below. (See Figure 2 for Neurosurgery/Spine Health History (intake questionnaire), Figure 3 for the SF-36, Appendix A for the Oswestry Disability Index and Appendix B for the Data Collection Tool, used to extract patient characteristic data from the medical record).

Patient Factors.

Patient factors examined in this study included patient characteristics in the categories of physiological factors (genotype, BMI, sex, age, smoking status), situational factors (employment status, worker's compensation claim and insurance type) and psychological factors (depression).

Physiological factors.

Body Mass Index.

BMI was calculated from the height and weight recorded in the spine service at the initial visit. Each patient is weighed at the initial visit. The height is reported by the patient. This information is recorded for each patient in the spine service on the last page of the Neurosurgery/Spine Health History (intake questionnaire). BMI is a continuous quantitative variable. Since height is recorded as reported by the patient and not measured directly, BMI may not be accurate, and this may be a limitation of the study.

Sex.

The sex of each patient is recorded at the time of the initial visit. This information is listed on the first page of the intake questionnaire. Sex is a categorical variable. Male or female was recorded for sex.

Age.

The birth date of each participant was extracted from the medical record. The birth date of each patient is used in the medical record as a patient identifier and validated with the patient, insurance sources and the referring provider's medical record by clinic administrative staff. The patient's birth date was recorded. Age is a discrete continuous variable.

Smoking status.

Since smokers have a higher incidence of back pain than non-smokers (Karahan, Kav, Abbasoglu & Dogan, 2009; Shiri, Karppinen, Lein-Arjas, Solovieva, & Viikari-Juntura, 2010), participant smoking status was extracted from the medical record. Each patient's smoking status was recorded at the time of the initial visit. This information is listed on the fourth page of the spine service intake questionnaire. The individual's current smoking status was recorded as yes/no. Since smoking status is self-report, this may be a study limitation. Smoking status is a categorical variable.

Genotype.

Saliva samples were collected by the primary investigator at the spine service at the Hauenstein Neuroscience Center as a DNA source for genotyping. Once full physiological, situational and psychological data, symptoms and outcome measures were identified for the desired number of study subjects, a random subset 30 of these subjects was identified and contacted for genotyping. Known variants within two candidate genes for pain experience (*OPRM-1* and *COMT*) and within four candidate genes for disc structural integrity (*COL9A2*, *COL9A3*, *ACAN* and *VDR*) were genotyped. Genotyping data are categorical. Physiological, situational and psychological factor data, symptom and physical function outcome data were collected from retrospective chart review from the first visit at the spine service, with baseline data collected from 2009-2012. Saliva samples for genotyping were collected in February, 2014. This time lapse between data collection times should not be a limitation of the study because genotype does not change over time (See Procedures section at the end of this chapter for specific genotyping procedures).

Situational factors.

Situational factors conceptualized in the TOUS include marital and employment status, access to health care, diet, exercise and social support (Lenz, Pugh, Milligan, Gift & Suppe, 1997). The situational factors conceptualized to interact with symptoms to affect physical function in this study included employment status, worker's compensation claim and insurance type.

Employment status.

Participant employment status was obtained from the medical record at the time of the first visit to the spine service. Employment status is recorded by the patient at the time of the initial visit on the spine service intake questionnaire (pg. 4, Appendix A). Employment status was recorded as employed/not employed. If an individual has recorded their status as retired or disabled, this was recorded as not employed. Employment status is a categorical variable. Employment status is self-report, and may be a study limitation.

If the individual had a worker's compensation claim related to the reason for their spine service visit, this was recorded and validated by clinic administrative staff prior to the time of the initial visit and noted in the payer information in the medical record. This information is also listed on the fourth page of the patient's intake questionnaire. If the patient presented to the spine service for care as a worker's compensation claim, this was recorded as "yes". If the patient presented to the spine service for care unrelated to a worker's compensation claim, this was recorded as "no". Since worker's compensation information is validated by administrative staff, the accuracy is not dependent on patient report. Worker's compensation claim is categorical data.

Insurance type.

Participant insurance type data was extracted from the medical record at the time of the first visit to the spine service. Insurance type is validated for each patient at each visit by clinic administrative staff and recorded on the patient's chart. Insurance type was recorded as commercial, Medicaid, Medicare, Tricare, or none. If the patient had more than one insurance policy, the primary insurance was recorded. Since insurance type is validated by administrative staff, the accuracy is not dependent on patient report. Insurance type is categorical data.

In summary, all physiological (except genotype) and situational factors were identified from the medical record at the time of the first visit to the spine service. These variables included BMI, sex, age, smoking status, work status, worker's compensation claim and insurance type. See Appendix D for the Data Collection Tool used to record the physiological and situational patient characteristics obtained from the medical record. Some data were dependent on patient self-report, and may represent a study limitation. Genotype data were collected in some cases as many as four years after the other data.

Psychological factors.

Psychological factors conceptualized in the TOUS include mental state or mood, affective reaction to illness, and uncertainty about the symptoms and their meaning (Lenz, Pugh, Milligan, Gift & Suppe, 1997). The psychological factor conceptualized to interact with symptoms to affect physical function in this study is depression.

Depression.

The presence of various psychological problems was recorded for each patient at the time of the first visit as part of the past medical history. The medical history section is on page two of the intake questionnaire. The medical history section allows patients to check a box next to the

medical problem, if present. Depression is specifically included in this list. The review of systems section on the intake questionnaire also includes a list of psychological problems, including depression, anxiety, bipolar, and "other". The review of systems list instructs patients to check a box next to the psychological problem, if present. The review of systems is on the second page of the intake questionnaire. Medical records from the referring provider are also received before the first clinic visit. Medical records from the primary care provider include information on the individual's past medical history. If the referring provider indicated a history of depression, it was considered to be present. Depression was recorded as yes/no, using the medical records from the referring provider. Depression is a categorical variable. In summary, depression was considered to be present if the referring provider's notes indicated depression as part of the medical history. See Appendix D for the Data Collection Tool.

The study is limited because depression was not measured directly. However, scores from the mental health subscale of the SF-36 were recorded, and the study population average mental health scores were compared to population norm values as well as published population values for lumbar degenerative conditions. This was done in order to compare the study population to published norms for mental health.

Symptoms.

Pain.

The intake questionnaire includes a horizontal pain visual analog scale, (VAS). Patients are instructed on the intake questionnaire to circle the number, (0-10) that best corresponds to their current pain level. Patients are asked to record their current pain on an 11 point horizontal line from 0 (no pain at all) to 10 (the worst pain you can imagine). The VAS score circled was

recorded. If more than one number was indicated by the participant, the average score was recorded, to the nearest .5. The VAS is on page one of the intake questionnaire, Appendix A.

The VAS is a pain intensity measure (Jensen, Karoly & Braver, 1986). The VAS is brief and easy to administer and score, produces interval-level data, and has been used across a wide variety of clinical conditions, including acute and chronic pain states (McGuire, 1997). Although there is some concern over the ability of persons to conceptualize pain in a linear fashion, the tool is considered reliable and valid (McGuire, 1997).

Validity of the VAS has been explored by comparing it to other methods of reporting pain intensity. Pearson correlation coefficients for the VAS compared with McGill Pain Questionnaire sensory, affective and evaluative scales has been reported as 0.49, 0.42, and 0.57, respectively, in a population of cancer patients (Ahles, Ruckdeschel & Blanchard, 1984). Correlation coefficient for the VAS and a verbal rating scale in a cancer population has been reported as 0.81 (Ohnhaus & Adler, 1975). Similarly, the correlation coefficient between the VAS and a numeric pain scale in a cancer population has been reported as 0.92 (Ahles, Ruckdeschel & Blanchard, 1984). Correlation coefficients comparing the horizontal VAS with the vertical VAS, a numeric pain rating score, and a simple descriptive score for pain in a population with rheumatic diseases were reported at 0.907, 0.616, and 0.726, respectively (Downie, Leatham, Rhind, Wright, Branco & Anderson, 1978). The VAS has demonstrated greater sensitivity than a simple descriptive scale (Scot & Huskisson, 1974; Downie, Leatham, Rhind, Wright, Branco & Anderson, 1978).

Test-retest reliability comparing scores on days one, three and five with days two, four and six was 0.78 in the same population of cancer patients (Ahles, Ruckdeschel & Blanchard, 1984). The VAS was one of the five most utilized instruments out of eleven pain scales studied

in a systematic review of pain instruments for use in chronic low back pain (Chapman et al., 2011). The VAS was determined to be reliable and responsive in this population, but the authors did not report reliability statistics. Chapman, et al. (2011) did not identify floor or ceiling effects with the VAS. The VAS was highly correlated with a verbal rating score for pain in a population of 85 patients with chronic pain ($r = 0.906$, $p < 0.001$) (Cork, et al., 2004).

Cut points for pain intensity have been studied in populations of cancer patients and patients having undergone amputation of a lower limb who were also experiencing low back pain. Pain levels 1-4 correspond to mild pain, 5-6 correspond to moderate pain, and 7-10 correspond to severe pain (Jensen, Smith, Ehde & Robinsin, 2001; Kathy, Harris, Hadi & Chow, 2007; Serlin, Mendoza, Nakamura, Edwards & Cleeland, 1995).

New spine patients are asked to complete an anatomic symptom diagram on the intake questionnaire. An anatomic diagram of the human body, with both anterior and posterior views, appears on page three of the spine service intake questionnaire. Patients are instructed to place symbols on the anatomic drawing where their pain is located. A pain diagram overlay was used to record the precise location of the patient's pain as described by Werneke, Hart and Cook (1999) and Cleland, Childs, Palmer and Eberhart (2006). The overlay assigns numbers 1 through 6, corresponding to the anatomic location of the pain from the low back, through the buttock, and into the leg. Every number correlating to the patient's location of pain on the anatomic diagram was recorded for data analysis. Pain below the gluteal fold was considered lower limb pain, consistent with the Quebec Task Force guidelines described in Atlas, Deyo, Patrick, Convery, Keller and Singer (1996) and Werneke and Hart (2004). Pain indicated in areas 1 and 2 was considered back pain for data analysis. Pain in areas 3, 4, 5 and 6 was considered leg pain for

data analysis, consistent with Quebec Task Force Guidelines (Atlas, Deyo, Patrick, Convery, Keller & Singer, 1996; Werneke & Hart, 2004).

Numbness.

Lower limb numbness can be a symptom associated with irritation of a lumbar spinal nerve root from degenerative changes described previously in Chapter 3. As part of the spine service intake questionnaire, patients are asked to complete an anatomic symptom diagram for pain and numbness. An anatomic diagram of the human body, with both anterior and posterior views, appears on page three of the intake questionnaire. Along with the anatomic drawing, there are explicit instructions for the patient, showing the symbols to use for the symptoms pain and numbness. The patient is instructed to place the appropriate symbol for pain and/or numbness at the location on the body part where the symptom is experienced. The presence of numbness was also determined by review of the dictated note from the spine service provider at the patient's initial clinic visit. The presence or absence of the symptom leg numbness in locations 3, 4, 5 or 6 was recorded as yes/no, respectively. Numbness was considered as a separate symptom in the data analysis. Since numbness in the low back is non-anatomic for a nerve root distribution, numbness in the low back was not recorded for data analysis. Numbness is a categorical variable. Numbness was determined from both the spine service provider's office dictation and from patient report, which strengthens the validity of this measure.

Weakness.

Motor strength is evaluated for each patient at the initial visit to the spine service. Motor strength is assessed by the provider on the first visit to the spine service during the physical exam and documented in the provider's dictation of the visit. Weakness was recorded as yes/no. The presence of weakness was obtained from the medical record. Weakness is a categorical variable.

In summary, symptom information was obtained from the medical record. Pain information was obtained from the VAS and the symptom diagram completed by the patient on the initial visit to the spine service. Information about numbness was obtained from the symptom diagram and provider documentation in the medical record. Information about weakness was obtained from the provider documentation in the medical record. See Table 1 for a list of study variables and sources.

Table 1
Study Variables

Variable Category	Variable Name	Variable Source	Variable Type
Physiological Characteristics	BMI	Medical Record	Quantitative
	Age	Medical Record	Quantitative
	Sex	Medical Record	Categorical
	Smoking Status	Medical Record	Categorical
Situational Characteristics	Employment Status	Medical Record	Categorical
	Worker's Compensation Claim	Medical Record	Categorical
	Insurance Type	Medical Record	Categorical
Psychological Characteristic	Depression	Medical Record	Categorical
Symptoms	Pain VAS	Medical Record	Quantitative
	Back Pain	Medical Record Pain Diagram (with overlay to measure)	Categorical
	Leg Pain	Medical Record Pain Diagram (with overlay to measure)	Categorical
	Numbness	Medical Record Pain Diagram and Provider Dictated Notes	Categorical
	Weakness	Medical Record Provider Dictated Notes	Categorical
Genotype (Physiological Characteristic)		Saliva Sample	Categorical
Physical Function Outcome Variables	ODI	Spine Service Password Protected Excel File	Quantitative
	SF-36 Physical Function Subscale	Spine Service Password Protected Excel File	Quantitative

Physical Function.

Physical function status was measured by scores on the ODI and the physical function subscale of the SF-36. ODI and SF-36 raw data for Spine Service patients have been entered onto an excel spreadsheet in the spine service office. The data are contained in a password-protected file. Only the primary investigator had access to the password. Once complete data on patient characteristics, symptoms, and physical function were identified for an adequate number of participants, data were cleaned, and raw data were scored according to ODI and SF-36 scoring instructions.

Oswestry Disability Index (ODI).

The ODI was used to measure physical function (Fairbank, Couper, Davies & O'Brien, 1980). The ODI is a 10-item disease-specific instrument for the lumbar spine population and is widely used as an outcome measure for patients with lumbar degenerative conditions (Roland & Fairbank, 2000). Although the authors of the original version hold the copyright, they do not require permission for its use (Roland & Fairbank, 2000). See Appendix C for the ODI.

The ODI takes approximately five minutes to complete and one minute to score. Two items address pain and the remaining eight items focus on how activities of daily living are affected by pain (Monticone, et al, 2009). Each item has six response levels, 0-5. The total numeric score is doubled and expressed as a percentage. The sum of the 10 scores is expressed as a percentage of the maximum scores, ranging from 0-100. Lower scores reflect better function.

The ODI has been found to be reliable, with intra-class correlations reported to be 0.84-0.94 (Davidson & Keating, 2002; Fritz & Irrgang, 2001). The ODI has high correlation (.77), with another lumbar functional instrument, the Roland-Morris Disability Questionnaire (RMDQ) (Fairbank & Pynsent, 2000). Internal consistency is demonstrated by Cronbach's Alpha ranging

from 0.71-0.87 (Roland & Fairbank, 2000). Reproducibility at 24-hour intervals was reported as $r = 0.99$, at four days as $r = 0.91$, and at one week as $r = 0.83$ (Roland & Fairbank, 2000). Because the ODI measures a clinical condition that can vary from day to day, the reduction in reproducibility scores may reflect natural fluctuations in the individual's spine condition. Test-retest reliability has been reported to range from 0.83-0.99 (Fairbank & Pynsent, 2000).

Evidence also exists for the validity of the ODI. Comparing ODI change scores to individual's global rating of change, the ODI ranked best out of all the outcome measures tested, $r = -0.64$, $p < 0.01$ (Taylor, Taylor, Foy & Fogg, 1999). A systematic review of multiple spine outcome measures found the ODI to be valid and highly correlated with the RMDQ, but the correlation coefficient and significance were not reported in this review article (Chapman et al., 2011).

The ODI was found to be comparable to other lumbar specific physical function instruments, including the RMDQ, Quebec Back Pain Disability Scale, the Waddell Disability Index and the physical function subscale of the SF-36, in responsiveness to change (Davidson & Keating, 2002). The responsiveness of the ODI has been demonstrated in individuals with acute and chronic low back pain. The correlations between positive ODI change scores and individual's estimations of improvements were 0.66 and 0.49 for the acute low back pain group and the chronic low back pain group, respectively (Grotle, Brox & Vollestad, 2004). In another large ($N = 970$) study comparing a disease-specific measure (the ODI), to the SF-36 in individuals with back and leg pain, the two instruments were similar in responsiveness (Receiver Operating Characteristic Curve = 0.723 and 0.721 for the ODI and the physical functioning subscale of the SF-36, respectively) (Walsh, Hanscom, Lurie & Weinstein, 2003).

Normative data with weighted mean scores on the ODI have been reported as 10.19 for normal populations, 26.63 in persons with spondylolisthesis, 36.65 in persons with neurogenic claudication, 43.3 in persons with chronic back pain, 44.65 in persons with sciatica, 44.83 in persons with fibromyalgia, and 48.04 in persons with spinal metastases (Roland & Fairbank, 2000). Scores from 0-20% reflect minimal disability, scores from 20-40% reflect moderate disability, scores from 40-60% reflect severe disability, scores from 60-80% reflect "crippled" state, and scores from 80-100% indicate the person is "bedbound or exaggerating" (Fairbank, Couper, Davies & O'Brien, 1980).

Medical co-morbidities can affect ODI scores. Baseline survey results from a large data set (N = 26, 290) were regressed with co-morbidities and patient characteristics. Although the investigators report that ODI scores decreased at baseline from an average of 62.4 to 42.0 for individuals with no and ≥ 7 co-morbidities, respectively (this would actually represent an improvement on the ODI), the regression analysis results table showed that poor self-rated health and the presence of worker's compensation had the most negative impact on ODI scores, with depression and smoking also having a significantly negative effect (Slover, Abdu, Hanscom, Lurie & Weinstein, 2006).

An expert panel convened to discuss a special issue of *Spine* devoted to measurement recommended that whenever possible, a condition-specific instrument for back pain should be used, specifically, either the ODI or the RMDQ (Roland & Fairbank, 2000). Two systematic reviews of lumbar-specific outcome instruments found the ODI and the RMDQ to be the most comprehensively validated functional measures for responsiveness (including improvement and deterioration in status), reliability and validity Chapman, et al., 2010; Cleland, Gillani, Bienen &

Sadosky, 2010). The total ODI score (the sum of the 10 scores expressed as a percentage of the maximum score) was used as an outcome measure.

Physical function subscale of the SF-36.

The Short Form-36 (SF-36) is a multi-purpose health survey that yields two component summary scores (i.e. the physical component summary and mental component summary) and eight subscale scores, including physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health. The SF-36 was developed to monitor health status of individuals with chronic health and psychiatric conditions over time (Tarlov, Ware, Greenfield, Nelson, Perrin & Zubkoff, 1989). Higher scores in each subscale or the total survey reflect better function. The physical function subscale scores are standardized such that the general U.S. population average scores are 50, with a standard deviation of 10 (Beaton & Schemitsch, 2003). See Appendix B for the SF-36.

The SF-36 has been used extensively across a wide range of clinical conditions and populations. It is widely used in orthopaedics and spine surgery. Many studies examining physical function as an outcome use the physical component summary scores and the physical functioning subscale scores.

The SF-36 physical function subscale has been demonstrated to be reliable. In a population with low back pain followed over a 6 week period, intra-class correlations (ICC) were 0.83 and 0.91 for the SF-36 physical function scale for groups estimating they were “unchanged” and “about the same”, respectively (Davidson & Keating, 2002). Patrick, Deyo, Atlas, Singer, Chapin & Keller (1995) reported a similar ICC of 0.89. The SF-36 was specifically used to test psychometrics in individuals with rheumatoid arthritis and osteoarthritis participating in a placebo-controlled drug trial after a 3-14 day washout period (Kosinski, Keller, Hatoum, Kong &

Ware, 1999). Internal consistency for all the subscales ranged from 91.4%-97.1%, and item discriminant validity ranged from 96.9%-100.0%. For the physical function subscale, item internal consistency ranged from 0.37-0.80, and reliability ranged from 0.89-0.91. Although the authors found the distribution of scores for the physical function subscale (and others) positively skewed in this population, floor and ceiling effects were observed only for the subscales of role physical and role emotional (Kosinski, Keller, Hatoun, Kong & Ware, 1999).

There is evidence for the validity of the physical function subscale of the SF-36. The physical function subscale is similar to the RMDQ (Patrick, Deyo, Atlas, Singer, Chapin & Keller, 1995; Davidson & Keating, 2002). Large effect sizes (≥0.80) were found after orthopedic surgery in the SF-36 subscales of physical function, role physical and bodily pain and small (0.20-0.49) to moderate (0.50-0.79) effect sizes were found in the subscales measuring mental and social aspects (Busija, Osborn, Nilsdotter, Buchbinder & Roos, 2008).

The standard version of the SF-36 has been designed for administration at four week intervals. There are normative data available for many different health conditions. The instrument has been translated into 121 languages. Shorter versions of the instrument have been developed, including the SF-12 and SF-8 (Ware, 2003). The SF-36 and its scoring software are copy-righted and must be purchased.

The presence of co-morbidities and other patient characteristics can change SF-36 scores. In patients with no co-morbidities, average change scores on the physical function subscale were 16.8, but with four co-morbidities, the average change scores decreased to 6.9 (Slover, Abdu, Hanscom & Weinstein, 2006). Physical function subscale change scores were most negatively impacted by headaches, poor self-rated health and age (Slover, Abdu, Hanscom & Weinstein, 2008). See Appendix A for ODI and SF-36 instruments. Physical function subscale scores were

used as an outcome measure, in addition to the ODI total score. Mental health subscale scores were also recorded, in order to compare study participant average with known population norms and normative scores for individuals with lumbar conditions.

Medications.

Because the use of analgesic medications can affect the experience of pain, analgesic use was also recorded on the data collection instrument. Five categories of medications were recorded, including non-steroidal anti-inflammatories, steroids, narcotics, other analgesics, and anti-convulsants such as gabapentin and pregabalin, often used to treat neuropathic pain.

Procedures

The dissertation proposal was approved by the student's Dissertation Committee. Grant funding was awarded by the Saint Mary's Foundation for resources to accomplish the exploratory Aim 3, involving genotyping. The study was approved by expedited review by the Mercy Health Saint Mary's Institutional Review Board (IRB # 13-1816-01-SM). A Reliance Agreement exists between Mercy Health Saint Mary's and Michigan State University. Eligibility criteria were: 1) aged 18 years or older, 2) back and/or leg complaints of pain, numbness, and/or weakness, 3) completed SF-36 and ODI information at first clinic visit, 4) complete information on selected patient factors and symptoms, including a completed anatomic pain drawing, 5) English-speaking. All eligible persons with lumbar degenerative conditions were included. Exclusion criteria were: 1) spinal cancer (primary or metastatic), 2) myelopathy or cauda equina syndrome, 3) major psychiatric disorder (personality disorder, schizophrenia and bipolar illness), 4) spinal fracture, 5) spinal infection, 6) being scheduled for surgery, 7) pain in the neck and upper extremities, 8) lumbar surgery within the last year, and 9) current pregnancy.

Recruitment Procedures for Aims 1 and 2.

Since the data needed to address Aims 1 and 2 were available from the medical record in the spine service, no recruitment of subjects for these aims was required. These subjects were identified by the primary researcher from the database of approximately 1,300 completed ODI and SF-36 questionnaires in the spine service. A computer program for random numbers was applied to the excel sheet containing patients with completed ODI and SF-36 questionnaires to arrange individuals in a random order. The medical records were reviewed proceeding from the beginning of this randomly arranged list for all of the data required to address Aims 1 and 2. If the necessary data on patient characteristics and symptoms were incomplete in the medical record, the next subject on the randomly arranged list was selected. This process was followed until complete data for patient characteristics and symptoms were collected for 163 subjects on the data collection sheet, more than the minimum number required for statistical analysis. This was done to assure sufficient data. Once complete data on patient characteristics and symptoms for 163 participants were identified the ODI and SF-36 physical function and mental health subscale raw data was cleaned and then scored according to guidelines. All data for each patient characteristic and outcome were then entered into an excel sheet for data analysis, with coded patient identifiers.

Recruitment Procedures for Aim 3.

When 163 subjects with complete data on patient characteristics were identified from the database of completed outcome measures, a subset of 30 individuals was selected from this population for the exploratory genotyping aim using the same computerized method to randomly arrange the 163 subjects from Aims 1 and 2. These individuals were contacted by phone by the primary investigator. Using a script, potential participants in the genotyping aim were informed

of the study and purpose and were invited to provide saliva samples. A minimum of two attempts were made to contact each potential subject for Aim 3, using mobile or home phone numbers. Subjects who traveled to the spine service to provide a saliva sample were provided a $10 gift card to a local retailer.

Subjects who agreed to provide a saliva sample were given a telephone number to contact the primary investigator to cancel or reschedule the appointment time, if necessary. Subjects calling to cancel were given the opportunity to reschedule. If the subject declined to reschedule, the next subject identified on the random list was contacted. The primary investigator continued to contact potential subjects from the randomized list for genotyping until 30 subjects agreed to provide saliva samples. The investigator telephoned 105 potential subjects in order to arrange saliva collection from the desired 30 participants for Aim 3. Each time a participant cancelled a saliva collection appointment, the next potential subject on the random list was contacted. If a subject failed to show for saliva collection, one attempt was made by telephone to re-schedule. This process continued over the course of two weeks. Saliva samples were successfully collected from 28 participants, but two participants either cancelled, or declined after arriving on the last day of saliva collection.

When the primary investigator met with subjects to collect the saliva sample, an eight page informed consent form was used to describe the dissertation study, (including the aims and significance) and the potential risks to participants. Subjects were assured of confidentiality. HIPAA authorization was included in the informed consent. Subjects signed the informed consent form prior to providing a saliva sample. The investigator was present to answer questions and provide clarification if needed. Procedures for collection of biological samples were reviewed, using the instructions provided with the Oragene OG-500 saliva collection kits.

Consents were stored in a locked cabinet at the spine service, accessible only to the primary investigator. If participants failed to show for a scheduled time to provide a saliva sample, a phone contact was made to inquire about rescheduling. If the participant declined to reschedule, the next subject identified by the table of random numbers was contacted.

Data Collection Procedures.

Saliva samples were obtained from subjects at the spine service. Although DNA yields are lower in saliva than blood, saliva DNA yields are sufficient for Taqman assays (Abraham et al., 2012). Saliva as the source for DNA was chosen because it was easier to collect and did not involve a venipuncture procedure. Saliva samples are stable at room temperature and were stored in the Clinical Trial Unit at Saint Mary's until transport to Michigan State University Genomics Core Facility, after a Materials Transfer Agreement was signed by both Mercy Health Saint Mary's legal representatives and the Michigan State University Technologies office. Only one type of saliva collection method was used, reducing potential variation in protein composition in saliva (Mohamed, Campbell, Cooper-White, Dimeski & Punyadeera, 2012; Golatowski, et al., 2013). A data use agreement has been signed by the investigator, Michigan State University and Mercy Health Saint Mary's.

Genotyping Procedures.

Saliva samples were stored at Mercy Health Saint Mary's Clinical Trials Unit in a locked specimen storage room until data collection for Aim 3 was complete. The investigator accessed this storage room only by admittance by Clinical Trials Unit staff. Saliva samples then were transported to the Michigan State University Genomics Core Facility by the investigator directly to Michigan State Core Genomics lab staff for processing and genotyping.

Saliva samples were processed using the Oragene DNA OG-500 kits (DNAGenotek, Ontario, Canada). An average 35-40µg of high quality DNA/1ml can be extracted from saliva. After establishing DNA sample yield and purity through spectrophotometry and PCR amplification, DNA samples were split and stored at –20°C for immediate access and at –80°C for back-up. The stability of Puregene and Oragene-purified genomic DNA is verified to at least 11 years (Puregene Product Information, www.gentra.com; Oragene Product Information, www.dnagenotek.com/). Subsequent genotyping was conducted using the Taqman® PCR platform (Applied Biosystems, Carlsbad, CA) for all variants except the *ACAN* VNTR polymorphism and the COL9A2 polymorphism. The *ACAN* VNTR was genotyped according to the methods described by Eser and colleagues (2010). COL9A2 (rs2228564) was genotyped using direct sequencing. See Table 2 for specific candidate genes and Single Nucleotide Polymorphisms (SNPs).

A study manual was created to include all procedures, scripts for patient contacts, and data collection tools for all study variables. The primary investigator was responsible for all data collection procedures, thereby ensuring consistency. See Appendix D for data collection tool.

Table 2
Genes Selected for Genotyping with SNPs (Single-Nucleotide Polymorphisms) Tested

Gene Acronym Locus	SNP rs#	Major/Minor Allele	MAF
COL9A2 1p34.2	rs2228564	A/C/G/T	0.385 (C)
COL9A3 20q13.33	rs61734651[a]	C/T	0.080 (T)
ACAN 15q26.1	Exon 12 VNTR	variable	variable
VDR 12q13.11	rs731236[b]	C/T	0.264 (C)
OPRM1 6q25.2	rs1799971	A/G	0.348 (C)
COMT 22q11.21	rs4680[c]	A/G	0.389 (A)

[a]also referred to asTrp3 allele in some studies.
[b]also referred to as VDR Taq1 allele in some studies.
[c]also referred to as val158met in some studies.
MAF = minor allele frequency

Data Management.

SF-36 and ODI raw data for spine service patients have been entered onto an excel spreadsheet on a spine service computer. The data are contained in a secure, password-protected file on the hospital hard drive. Only the primary investigator had access to the password. Identifiable patient data was not stored on a personal laptop. Identifiable patient data was not stored on a flash drive. Identifiable patient data was coded prior to statistical analysis. ODI and SF-36 raw data was converted into subscale scores with proprietary scoring instructions from the user's manuals.

The medical record was reviewed for patient characteristics and symptoms, and this data was recorded onto the patient characteristics and symptoms data collection instrument. These activities occurred within the spine service office by the primary investigator. All procedures are detailed in a study procedures manual, which contains information on the study, scripting for initial phone contact with eligible persons, all study data collection instruments, and steps in the

study process. Data cleaning and entering from the ODI and SF-36 was completed by the primary investigator.

For Aim 3, saliva samples were collected in person from consenting subjects by the primary investigator. Saliva was collected according to instructions provided by the manufacturer. Saliva sample containers were labeled with the coded number assigned to the subject and no patient identifiers were used on the saliva sample container. The collected saliva samples were stored at room temperature in the Clinical Trials Unit at Mercy Health Saint Mary's until all samples were collected. The saliva samples were then transferred to the Core Genomics Facility at Michigan State University by the investigator after a Material Transfer Agreement was signed between the two institutions.

Data Analysis.

Summary statistics were created to describe the population. Descriptive statistics were used to describe the population on the characteristics of physiological factors (genotype, BMI, age, sex, smoking status), situational factors (employment status, workers compensation claim, and insurance status), and psychological factors (depression). Assumptions for normality, lack of extreme outliers, multicollinearity, homoscedasticity, and linearity were checked.

Aim 1 Specific Strategies: To determine the contribution of physiological (BMI, sex, age, smoking status), situational (employment status, worker's compensation claim, insurance type), and psychological (depression) factors in persons receiving non-surgical interventions for degenerative lumbar conditions to symptoms and physical function.

In the specific Aim 1 analysis, the independent variables include BMI, sex, age, smoking status, employment status, workers compensation claim, insurance type, and depression. Symptoms, including pain (location in back only or back and leg) numbness in the leg, and

weakness were treated as both dependent variables and independent variables in separate statistical testing. Physical function is considered the dependent variable, as measured by the scores on the ODI and the physical function subscale of the SF-36.

In the specific Aim 1 analysis, descriptive statistics were used to describe the population on the characteristics of physiological factors, situational factors, psychological factors, and symptoms. Although depression was not measured directly, SF-36 mental health subscale scores for the study population were compared with population norms. Multivariate methods (multiple regression) was used to examine the contribution of patient characteristics to symptoms and to physical function. Multiple regression was also used to examine the contribution of patient characteristics and symptoms to scores on the ODI and physical function subscale of the SF-36.

Aim 2 Specific Strategies: Develop a predictive model for the outcome of physical function in persons receiving non-surgical interventions for lumbar degenerative conditions, using symptoms (back and/or leg pain, numbness, and weakness) and physiological, situational, and psychological patient factors.

In the specific Aim 2 analysis, multivariate methods were used to identify how patient characteristics and symptoms combine to predict physical function.

Exploratory Aim 3 Specific Strategies: Explore the impact of the physiological factor genotype (disc structural genes and pain genes) on symptoms (back and/or leg pain, numbness, and weakness) and on physical function in persons experiencing lumbar degenerative conditions.

In the specific exploratory Aim 3 analysis, genotype data on *COMT, OPRM-1, ACAN, VDR, COL9A2 and COL9A3* was analyzed. Descriptive statistics were used to describe the allele and genotype frequencies for each polymorphism. Multivariate statistics (multiple regression)

were used to examine the contribution of genotype to symptom experience and genotype to physical function.

Limitations.

Limitations of this study include the descriptive, cross-sectional design and the use of secondary data. This limited the ability to establish a temporal relationship between the predictors and the outcome. This study is also limited by the use of a convenience sample, limiting generalizability of the findings. The presence of depression was based on review of the medical record in this study and not measured directly. The validity of this variable and the interpretation of its significance in this study were therefore limited. Future prospective studies with this population should be planned measuring depression directly with reliable and valid instruments. Data on patient characteristics, symptoms and physical function predates genotyping data by as many as four years, which should not affect interpretation of results because genotype does not change over time.

This dissertation study organizes and examines salient antecedent physiological, situational and psychological factors and symptoms and how they interact to influence physical function in individuals with lumbar degenerative conditions. Considering genotype to be a physiological antecedent factor is consistent with the concepts and propositions of the TOUS, and represents an innovative incorporation of biomarkers with patient characteristics and symptoms and their influence on outcome in this population.

Human Subjects.

Human subjects characteristics and involvement.

The study sample includes persons referred to the Spine Service at the Hauenstein Neuroscience Center at Mercy Health Saint Mary's from February 2009 through early 2012, with back and/or leg pain. All English-speaking patients aged 18 or older, referred to the spine service with back and/or leg pain and complete data for outcome measures and patient characteristics were eligible to be included in the study population. Women, men and minorities had equal chance of being represented in the study population, as did disadvantaged patients, since the mission of Mercy Health Saint Mary's includes care to the underserved. The Hauenstein Neuroscience Center (including the spine service) does not provide care to children (persons under the age of 18).

The spine service at the Hauenstein Neuroscience Center has a data base that includes completed ODI and SF-36 questionnaire responses from approximately 1,300 patients. Inclusion criteria are: 1) aged 18 years or older, 2) back and/or leg complaints of pain, numbness, and/or weakness, 3) completed SF-36 and ODI information at first clinic visit, 4) complete information on study variables patient characteristics and symptoms, including a completed anatomic pain drawing, and 5) English-speaking. A specific radiographic diagnosis prior to presentation at the spine service is not required. Exclusion criteria are: 1) spinal cancer (primary or metastatic), 2) myelopathy or cauda equina syndrome, 3) major psychiatric disorder (personality disorder, schizophrenia, and bipolar illness), 4) spinal fracture, 5) spinal infection, 6) being scheduled for surgery, 7) pain in neck and upper extremities, 8) lumbar surgery within the last year, and 9) pregnant status. Prisoners, considered a vulnerable population in research, are not treated in the outpatient spine service.

Sources of material.

ODI and SF-36 data will be obtained from a password-protected file that contains baseline scores from more than 1,300 individuals treated in the spine service. Using a computer program to randomize the file containing baseline scores for ODI and SF-36 questionnaires, 163 subjects with complete data on outcome measures were identified from the database, slightly more than the target number of 154. The medical records of these individuals were reviewed for patient characteristics and symptoms. Subjects for genotyping were identified from the 163 study participants from Aims 1 and 2 by applying the same computer program to randomize the list of 163. DNA for genotyping was isolated from saliva samples collected from consenting subjects.

Potential risks.

Potential risks to subjects were minimal. The procedure of collecting saliva samples causes little to no discomfort and has a minimal possibility of infection. It is not anticipated that information generated through this research will affect the insurability of subjects. Insurance companies will not have access to this research data. Participants were informed that the genetic analyses performed during this study are not a form of treatment, diagnosis, or prediction of lumbar spinal degeneration. Therefore the results of the genetic studies were not reported to the participants nor were they placed in the subject's medical record.

Participation in this study may cause anxiety related to increased awareness of the genetic contributions to lumbar degenerative conditions. Basic education and reassurance regarding the multi-factorial nature of lumbar spinal degeneration was provided by the primary investigator, if necessary. Referrals for genetic and psychological counseling were not made.

Protection against risk.

Several strategies to protect human subjects were implemented. Saliva samples were collected by the primary investigator. In the event of psychological or emotional distress related to an increased awareness of lumbar spinal degeneration heritability, subjects had access to basic education regarding the multi-factorial nature of lumbar spinal degeneration from the PI. In addition, several safeguards to ensure privacy of data were undertaken. Coded ID numbers were used on the saliva collection containers, DNA sample vial and genotype reports. Any flash drives with subject information were coded, to avoid identification of subjects. The code key linking names and ID numbers were kept separately from other data in a password protected file on the hospital hard drive only. All paper records were maintained in locked files in a locked research office. In addition, published reports of results will not include subject identifiers. Because the clinical usefulness of the candidate lumbar spinal degeneration genotype data remains experimental, results of the genotyping were not disclosed to subjects. Subjects were advised that they could withdraw their genotype data from the study analysis at any time without penalty. Following completion of this study, DNA samples were destroyed, in compliance with the Data Use Agreement between Mercy Health Saint Mary's and Michigan State University. See Appendix E for Data Use Agreement.

Participants maintained the right to withdraw from the study at any time without affecting their care at the spine service. Confidentiality of all findings, including genotyping results, was maintained.

Potential benefits of the proposed research to subjects and others.

While there were no anticipated direct benefits to subjects for participating in this study, the findings may enable health care providers to better predict persons at relatively high risk for

worse physical function outcome from a combination of individual characteristics (including genotype) and symptoms. Findings may also provide researchers with a better understanding of the genetic mechanisms contributing to decreased physical function in persons with lumbar degenerative changes. This understanding may lead to the development of improved interventions in the future. This chapter outlined the methods, variables, subjects, setting, sources of data, procedures, potential risks, human subjects protection and anticipated benefits. Chapter will discuss results.

CHAPTER V

Results and Interpretation

Organization of Results Chapter

The results chapter will be organized into sections that describe demographic information, patient characteristics and physical function status for study participants. Data analysis and findings will then be discussed, organized by study aim. Because of the large number of variables used in the multiple regression models, for the sake of brevity, only the full and final models are shown in the tables.

The population of subjects included in Aims 1 and Aims 2 will be referred to as the sample. The population of subjects included in Aim 3 will be referred to as genotyped subjects.

First, demographic descriptions of the study population will be discussed. Patient characteristics and symptoms will be described. Physical function status (ODI scores and physical function subscale scores for the SF-36) for the study population will be discussed. Next, data analysis and findings for Aim 1 will be reviewed. Aim 2 data analysis and findings will then be discussed. Other data analysis relevant to the review of the literature, the study population and the Aims of the study will also be reviewed.

The demographic description of genotyped subjects will progress in the same manner. Any significant differences between the two populations will be discussed. Last, Aim 3 data analysis and findings will be described.

Medical Records Reviewed

Patient characteristics data (BMI, sex, age, smoking, employment status, worker's compensation claim, insurance type and depression) were obtained from the medical record. Likewise, symptom data was obtained from the medical record from the subjects first visit to the

spine service during the time period 2009-2012. Specifically, the intake questionnaire was reviewed as well as the provider's dictated report of the initial clinic visit. Since many of the subjects had been evaluated in the spine service between 2009 and 2012, most of the medical records were retrieved from an off-site storage facility. The randomized list of subjects was sent to the storage facility by the medical records staff.

In order to ensure complete data for analysis for Aims 1 and 2 for the desired 154 subjects, medical records for 275 individuals were requested from the medical records staff at the Hauenstein Neuroscience Center at Mercy Health Saint Mary's. Out of the 275 medical records requested, 64 records (23%) could not be located by the medical records staff of the Hauenstein Neuroscience Center or by the staff of the storage facility where past medical records were kept. Another 48 medical records (17.5%) were excluded because they did not meet inclusion criteria, leaving 163 useable medical records (59%) for the study.

The reasons for exclusion were pain complaints not related to the lumbar spine, insufficient data on symptoms, patient characteristics, or outcome measures, and mental illness. Twenty- eight records (10%) were excluded because the clinical complaints were related to the cervical spine. Seven medical records (2.5%) were excluded because the pain visual analog scale was not completed. Six medical records (2.2%) were excluded because the pain diagram was not completed. Three medical records (1%) were excluded because of a diagnosis of bipolar illness or multiple personality disorder. Three other medical records (1%) were excluded because of incomplete data on an outcome measure and a patient characteristic, lumbar surgery within the previous year and age less than 18. One medical record (.03%) was quarantined and unavailable because of ongoing litigation.

There were therefore 163 medical records that met inclusion criteria and were included in the study. This number exceeded the desired study population of 154. However, since all of the medical records contained useable data, it was decided to include all of them in the study.

SF-36 physical function and mental health item responses were checked for missing and out of range responses. One subject's SF-36 physical function subscale responses were all missing but one, so this was treated as a missing variable. No subject had more than 3 missing responses for the SF-36 physical function subscale. These subscales were able to be scored, using the Half-Scale Rule, which states that if at least half of the subscale items have been answered, the subscale can be scored and used (Ware et al., 2007). The two mental health subscale responses requiring reverse coding were recoded according to scoring instructions (Ware et al, 2007). Physical function and mental health subscale scores were transformed into *z*-scores, and then to norm-based scores using the formulas from the *User's Manual for the SF-36v2 Health Survey* (Ware, et al., 2007). ODI scores were expressed as a percentage, according to scoring instructions for the ODI.

Demographic Information and Patient Characteristics for the Sample

The mean BMI for study subjects was 30.4 (S.D. = 8.41). Forty-eight subjects (29.4%) were considered overweight, with a BMI between 25 and 29.9. Forty-eight subjects (29.4%) were considered obese, with a BMI between 30 and 39.9. Twenty subjects (12.3%) had a BMI of 40 or greater, considered to be class III, or high risk obesity (National Institutes of Health, 2014). In summary, 71.1% of the subjects (n = 116) in the study population were overweight, obese, or Class III obese. See Table 3 for study population *N* and percent of overweight, obese and class III obese individuals.

Table 3
Sample *N* and % of Overweight, Obese and Class III Obese (*N* = 163)

BMI	*N*	%
Overweight (BMI >/= 25-29.9)	48	29.4%
Obese (BMI >/= 30-39.9)	48	29.4%
Class III Obese (BMI >/= 40)	20	12.3%

Nearly 58% of study subjects were female (*n* = 91). The mean age of study subjects was 54 (S.D. = 16.85). The youngest was 22 and the oldest was 93. The majority of subjects were younger than 65 (119 subjects, or 73%). Forty-four subjects (27%) were aged 65 or older. Twenty- eight percent of all study subjects (46) were current smokers/tobacco users. Among men, 35% (24) were smokers. Twenty-three percent (22) of women were smokers.

More than 56% (92) of the study subjects were not working at the time of presentation to the spine service. Among men, 52% (36) were not working. Sixty percent of women were not working (56). Among the 119 subjects younger than 65, 46% (55) were not working.

The majority of study subjects were covered by commercial insurance (57%, or 93 subjects). Medicare insurance accounted for coverage for nearly 21% of subjects (36), followed by 20 covered by Medicaid (12%), eight with no insurance (5%), three with auto (<2%), three with worker's compensation (<2%) and two with tricare (1%). Among the study subjects who were working, 87.32% (62) were covered by commercial insurance, 4.23% (3) had Medicare insurance, 4.23% (3) had Medicaid insurance, 2.82% (2) had no insurance and 1.4% (1) had auto insurance. See Table 4 for insurance coverage for the entire sample and for working subjects in the sample.

Table 4
Insurance Coverage for the Sample and for Working Subjects in the Sample

Insurance Type	Sample N and % (*N* = 163)	Working Subjects in the Sample N and % (N = 71)
Worker's Compensation	3 (1.84)	0
Commercial Insurance	93 (57.06)	62 (87.32)
Medicare	34 (20.86)	3 (4.23)
Medicaid	20 (12.27)	3 (4.23)
No Insurance	8 (4.91)	2 (2.82)
Auto	3 (1.84)	1 (1.4)
Tricare	2 (1.23)	0

Thirty-one percent (51subjects) had been diagnosed with depression, according to the clinical diagnosis from the medical record. Of the women, 38% (36 subjects) were depressed, while 22% of the men (15 subjects) were depressed. This difference was statistically significant ($x^2 = 5.075$, $p. = .024$).

Mental health subscale scores and depression were significantly related for the sample. Both parametric and non-parametric tests of association were used, because of one extreme outlier (*t*-statistic = 4.180, $p. = .000$; Mann-Whitney U test $p. = .000$). This finding helps strengthen the reliability of the variable depression for this study. See Table 5 for sample patient physiological, situational and psychological characteristics, *N* and percent for categorical variables. See Table 6 for sample patient physiological characteristics, range, minimum, maximum, mean and SD for BMI and age.

Table 5
Sample Patient Physiological, Situational and Psychological Characteristics, *N* and % for Categorical Variables (*N* = 163)

Category	Characteristic	Variable	*N*	%
Physiological	Smoking	Non-smoking	117	71.8
		Smoking	46	28.2
	Sex	Female	91	57.7
		Male	69	42.3
Situational	Work Status	Working	71	43.6
		Non-working	92	56.4
	Insurance Type	Commercial	93	57.1
		Medicare	34	20.9
		Medicaid	20	12.3
		Auto	3	1.8
		Worker's Compensation	3	1.8
		Tricare	2	1.2
		No Insurance	8	4.9
Psychological	Depression	Depressed (per medical record)	51	31.3
		Not Depressed	112	68.7

Table 6
Sample Patient Physiological Characteristics, Range, Minimum, Maximum, Mean and SD for BMI and Age (*N* = 163)

Category	Characteristic	Range	Sample Mean	SD
Physiological	BMI	15.81-71.04	30.44	8.41
	Age	22-93	54.07	16.85

Symptoms for the Study Population

The mean pain VAS for the sample was 6.83 (S.D. = 2.2). One individual had a pain VAS of 0. Women and men were similar with regard to the mean pain VAS. The mean pain VAS for women was 6.85 (S.D. = 1.99) and the mean pain VAS for men was 6.79 (S.D. = 2.46), not a statistically significant difference (*p*. = .861). Twenty-seven subjects (16.6%) reported weakness. Sixty-five subjects (40%) reported numbness. One subject reported no pain. Thirty-nine subjects (24%) reported back pain only. One hundred subjects (61%) reported back and leg pain. Twenty-three subjects (14%) reported leg pain only. See Table 7 for sample pain VAS mean, maximum, minimum and sex differences. See Table 8 for sample categorical symptoms of pain location, weakness and numbness.

Table 7
Sample Symptom Continuous Variable: Pain VAS (*N* = 163)

Symptom	Range	Min.	Max.	Sample Mean	SD
Pain VAS Study Sample	10	0	10	6.83	2.2
Females	8	2	10	6.85	1.99
Males	10	0	10	6.79	2.46

Table 8
Sample Symptom Categorical Variables: Pain Location, Weakness and Numbness (*N* = 163)

Symptom	*N*	%
Pain Location		
Back Pain Only	39	23.9
Leg Pain Only	23	14.1
Back and Leg Pain	100	61.3
Weakness		
No Weakness	136	83.4
Weakness	27	16.6
Numbness		
No Numbness	98	60.1
Numbness	65	39.9

Outcome Measures for the Sample

The mean ODI score for the sample was 50.96 (S.D. = 19.3) (range: 0-90). For the ODI, lower scores reflect better physical function. Scores between 40 and 60 reflect severe disability, (Fairbank, Couper, Davies & O'Brien, 1980). The mean ODI score for the sample is higher (worse) than published normative scores for individuals with spinal metastases, which is 48.04, implying that the study sample perceived themselves as having worse physical function than a population of subjects with spinal metastatic cancer (Roland & Fairbank, 2000).

Likewise, the mean physical function subscale score from the SF-36 for the sample was 32.57 (S. D. = 11.98) (range: 14.94-57.03). For the SF-36 subscales, higher scores reflect better function. Published healthy population norm score is 54.76 (S.D. = 6.04) (Ware et al., 2007). The sample mean physical function subscale score is lower than published mean score for individuals with back pain and sciatica (46.78, S.D. = 11.14). Moreover, the sample mean

physical function subscale score is worse than mean population scores of the 25th percentile for individuals with back pain and sciatica (40.87, S.D. = 11.14) (Ware et al., 2007). The sample score compares similarly to the mean population scores from the 25th percentile of those with diabetes (32.68, S.D. = 11.18), and is only slightly better than the 25th percentile for those with cancer (30.64, S.D. = 11.52) (Ware et al., 2007). See Table 9 for sample population physical function outcome scores for the ODI and the SF-36.

Table 9
Sample Physical Function Scores: Range, Minimum, Maximum, Mean and SD

Outcome Measure	*N*	Range	Sample Mean	SD
ODI	162	0-90	50.96	19.29
SF-36 Physical Function Subscale	161	14.94-57.03	32.58	11.62

The sample mean mental health subscale score from the SF-36 was 44.73 (S.D. = 14.4). Published healthy population norm score is 53.43 (S.D. = 8.38) (Ware et al., 2007). The mean score for a population with depression is 36.70 (S.D. = 11.08) (Ware et al., 2007). Therefore, while the sample mean mental health subscale score was higher than for those with depression, it was worse than the population norm. In fact, the sample mean mental health subscale score was worse than the mean score for individuals with back pain and sciatica (47.46, S.D. = 10.78), but slightly better than for those in the 25th percentile with back pain and sciatica (41.71, S.D. = 10.78) (Ware et al, 2007).

There were no statistically significant differences between men and women with regard to ODI, physical function subscale or mental health subscale scores using independent *t*-tests (*p*. = .765, .218, and .836, respectively).

In summary, the study population consisted of individuals who tended to be overweight. More than half of the study population was not working at the time of data collection. With a mean pain VAS just under 7 (on a 0-10 scale), the study population was experiencing severe pain. Finally, the perceived physical function of the study population was severely limited. A discussion of the analyses for Aims 1 and 2 will be presented in the following section.

Aim 1 Analysis

For Aim 1, to determine the contribution of physiological (BMI, sex, age, smoking status), situational (employment status, worker's compensation claim, insurance type), and psychological (depression) factors to symptoms and physical function, the relationships between patient characteristics and symptoms were examined first. Next, the relationship between patient characteristics and outcome measures (ODI and physical function subscale of the SF-36) were examined.

The relationship between patient characteristics and pain VAS.

Multiple regression was used to examine the contribution of BMI, sex, age, smoking, employment status and depression to pain VAS. Sex, age and depression were not significant in predicting pain VAS and were eliminated from the model early. BMI and employment status became insignificant in the model as well. Smoking was the only significant predictor of pain VAS. Smoking was associated with higher pain VAS scores but explained only 8.6% of the variance ($F = 15.066$, $p. = .000$). See Table 10 for coefficients, significance and R^2 for the full and the final models for predicting pain VAS using patient characteristics (BMI, sex, age, smoking, employment status and depression).

Table 10
Coefficients and Observed Levels of Significance for the Full and Final Multiple Regression Models for Predicting Pain VAS Using Patient Characteristics (BMI, Sex, Age, Smoking, Employment Status and Depression) (*N* = 163)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		Beta	Std. Error	Beta			
Full	(Constant)	5.337	.943		5.661	.000	0.118
	BMI	.029	.020	.113	1.476	.142	
	sex	.130	.345	.029	.377	.707	
	age	.005	.011	.038	.467	.641	
	smoking	1.408	.397	.289	3.542	.001[a]	
	employment status	-.469	.353	-.106	-1.328	.186	
	depression	.175	.373	.037	.470	.639	
Final	(Constant)	6.423	.195		32.940	.000	0.086
	smoking	1.425	.367	.293	3.881	.000[a]	

Dependent Variable = Pain Visual Analog Scale (VAS)
[a] indicates *p*-values < 0.10, [b] indicates *p*-values < 0.05, [c] indicates *p*-values < 0.001

Insurance types (commercial insurance, Medicare, Medicaid, worker's compensation and no insurance) were evaluated for effect on pain VAS using multiple regression, keeping in the final three patient characteristics of BMI, employment status and smoking from the previous model. Tricare was not included in this model, because only two subjects in the study population had this type of insurance. In the final model, smoking, having Medicaid insurance and not having insurance were all associated with higher pain VAS, explaining 13% of the variance (F = 7.907, *p*. = .000). See Table 11 for the coeffecients, significance and R^2 for the full and the final

regression models for predicting pain VAS using patient characteristics (BMI, employment status and smoking) and insurance type.

Table 11
Coefficients and Observed Levels of Significance for the Full and Final Multiple Regression Models for Predicting Pain VAS Using Patient Characteristics (BMI, employment status and smoking) and Insurance Type (*N* = 163)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		Beta	Std. Error	Beta			
Full	(Constant)	6.293	1.089		5.778	.000	.156
	BMI	.019	.021	.074	.924	.357	
	smoking	1.080	.410	.222	2.635	.009[a]	
	depression	.190	.372	.040	.512	.609	
	employment status	-.504	.396	-.114	-1.272	.205	
	workers compensation	-2.249	1.533	-.138	-1.467	.144	
	commercial insurance	-.302	.988	-.068	-.305	.760	
	medicare	-.405	1.020	-.075	-.397	.692	
	medicaid	.378	1.069	.057	.353	.724	
	noins	1.076	1.242	.106	.867	.387	
Final	(Constant)	6.319	.196		32.318	.000	.130
	smoking	1.018	.388	.209	2.624	.010[b]	
	medicaid	1.096	.519	.164	2.112	.036[b]	
	no insurance	1.731	.782	.171	2.213	.028[b]	

Dependent Variable = Pain Visual Analog Scale (VAS)
[a] indicates *p*-values < 0.10, [b] indicates *p*-values < 0.05, [c] indicates *p*-values < 0.001

The relationship between patient characteristics and weakness and numbness.

Logistic regression was used to examine the relationship between patient characteristics (BMI, sex, age, smoking, employment status and depression) and the symptoms of weakness and

numbness. Using a backward step-wise approach, age was the only statistically significant variable in the final logistic regression model for patient characteristics and weakness (Table 12). However, it had no discriminatory value, predicting weakness in every subject (Table 13). Using a backward step-wise approach, employment status was statistically significant in the final logistic regression model for patient characteristics and numbness (Table 14). However, its predictive value was only 60% (Table 15). Therefore, it was concluded that there were no patient characteristics with predictive value for the symptoms of weakness and numbness.

To determine the effects of patient characteristics on the symptom of pain location, the patient's documented location for pain, 1-6 was separated into the three clinically relevant categories of back pain, leg pain, and back pain with leg pain, consistent with Quebec Task Force Guidelines (Atlas, Deyo, Patrick, Convery, Keller & Singer, 1996; Werneke & Hart, 2004) and according to methods described in Cleland, Childs, Palmer and Eberhart (2006). Pain in areas 1 and 2 was considered back pain, and pain in areas 3-6 was considered leg pain. There was no statistically significant relationship between pain VAS and pain location with ANOVA ($F = .273$; $p. = .761$).

Table 12
Logistic Regression for Predicting Weakness Using Patient Characteristics, Full and Final Models (*N* = 163)

Step	Independent Variables	Beta	S.E.	Wald	df	Sign.	Exp(B)
1 (Full)	BMI	.018	.027	.437	1	.508	1.018
	sex	-.448	.447	1.006	1	.316	.639
	age	.016	.015	1.184	1	.277	1.016
	smoking	-1.244	.675	3.390	1	.066	.288
	employment status	-.143	.476	.090	1	.764	.867
	depression	.138	.501	.076	1	.783	1.148
	Constant	-2.537	1.313	3.734	1	.053	.079
6 (Final)	smoking	-1.308	.640	4.183	1	.041	.270
	Constant	-1.355	.229	35.002	1	.000	.258

Dependent Variable: Weakness
S.E.: standard error
Wald: Wald statistic
df: degrees of freedom
Exp(B): odds ratio

Table 13
Classification Table for Full and Final Logistic Regression for Predicting Weakness Using Patient Characteristics (*N* = 163)

Observed			Predicted		
			weakness		Percentage Correct
			no weakness	weakness	
Step 1 (Full)	weakness	no weakness	136	0	100.0
		weakness	27	0	.0
	Overall Percentage				83.4
Step 6 (Final)	weakness	no weakness	136	0	100.0
		weakness	27	0	.0
	Overall Percentage				83.4

Table 14
Logistic Regression for Predicting Numbness Using Patient Characteristics, Full and Final Models (*N* = 163)

Step	Independent Variables	Beta	S.E.	Wald	df	Sign.	Exp(B)
1 (Full)	BMI	.012	.020	.387	1	.534	1.012
	sex	-.119	.346	.118	1	.731	.888
	age	.010	.011	.875	1	.350	1.010
	smoking	.565	.402	1.977	1	.160	1.759
	employment status	.998	.359	7.714	1	.005	2.714
	depression	.455	.373	1.489	1	.222	1.576
	Constant	-2.033	.970	4.393	1	.036	.131
6 (Final)	employment status	.804	.327	6.058	1	.014	2.234
	Constant	-.776	.224	11.953	1	.001	.460

Dependent Variable: Numbness
S.E.= standard error
Wald = Wald statistic
df = degrees of freedom
Exp(B): odds ratio

Table 15

Classification Table for Full and Final Logistic Regression for Predicting Numbness Using Patient Characteristics (*N* = 163)

Observed			Predicted		
			Extremity numbness		
			no extremity numbness	extremity numbness	Percentage Correct
Step 1 (Full)	Extremity numbness	no extremity numbness	84	14	85.7
		extremity numbness	48	17	26.2
	Overall Percentage				62.0
Step 6 (Final)	Extremity numbness	no extremity numbness	63	35	64.3
		extremity numbness	29	36	55.4
	Overall Percentage				60.7

The relationship between patient characteristics and pain location.

Discriminant analysis was used to determine the effects of patient characteristics (BMI, age, sex, smoking, employment status and depression) on pain location. Only age and smoking had significant associations with pain location (F = 6.643, *p*. = .002 and F = 5.331, *p*. = .000, respectively). However, using the squared canonical correlations, age alone only accounted for 8% variance, and age and smoking together only accounted for 5% of the variance. See Table 16 for discriminant analysis using BMI, sex, age, smoking, employment status and depression to predict pain location (back pain only, back and leg pain, leg pain only). Chi-square was used to determine if sex and pain location, depression and pain location and worker's compensation were related, but there were no statistically significant relationships identified (x^2 = 1.943, *p*. = .584; x^2 = 3.042, *p*. = .385 and x^2 = 1.925, *p*. = .588, respectively). See Table 17 for chi-square tests using the categorical patient characteristics of sex, depression and worker's compensation as predictors of pain location. Only three subjects had worker's compensation insurance. With analysis of variance (ANOVA), there was no statistically significant relationship between BMI and pain location (F = .726, *p*. = .583). See Table 18 for analysis of variance for patient continuous variable BMI as a predictor for pain location. None of the patient characteristic variables predicted pain location. It was likely that that the sample was too small to model sufficiently using these variables.

Table 16

Discriminant Analysis Patient Characteristics (BMI, Age, Sex, Smoking, Employment Status and Depression) as Predictors of Pain Location (Back Pain Only, Back and Leg Pain, Leg Pain Only) (N = 162)

Patient Characteristic	Wilk's Lambda	F-statistic	Sign.	Eigenvalue	Canonical Correlation	Squared Canonical Correlation
1 Age	.923	6.643	.002[b]	.084	.278	.08
2 Age and Smoking	.878	5.331	.000[c]	.051	.221	.05

Dependent Variable: Pain Location

[a] indicates *p*-values < 0.10, [b] indicates *p*-values < 0.05, [c] indicates *p*-values < 0.001

Table 17

Chi-square Categorical Patient Characteristics (Sex, Depression, Worker's Compensation) as Predictors of Pain Location (Back Pain Only, Back and Leg Pain, Leg Pain Only) (*N* = 162)

Patient Characteristic	Chi-square	df	Sign.
Sex	1.943	3	.584
Depression	3.042	3	.385
Worker's Compensation	1.925	3	.588

Dependent Variable: Pain Location

df = degrees of freedom

Table 18

Analysis of Variance for Continuous Patient Characteristic (BMI) as Predictor of Pain Location (Back Pain Only, Back Pain and Leg Pain, Leg Pain Only) (*N* = 162)

Patient Characteristic (BMI)	Sum of Squares	df	Mean Square	F	Sign.
Between Groups	155.015	3	51.672	.726	.538
Within Groups	11315.630	159	71.167		
Total	11470.645	162			

Dependent Variable: Pain Location

df = Degrees of Freedom

Sign.: Significance

Groups: Back Pain Only, Back Pain and Leg Pain, Leg Pain Only

The relationship between patient characteristics and outcome measures.

Because there were two outcome measures, the ODI and the physical function subscale from the SF-36, separate statistical tests were used to explore the influence of patient physiological, situational and psychological characteristics on physical function. These tests will be reported separately.

Backward multiple regression was used to examine the effects of patient characteristics BMI, sex, age, smoking, employment status and depression on ODI scores. BMI, smoking and employment status were significant and explained 15.4% of the variance in ODI scores ($F = 9.621$, $p. = .000$). Being employed was associated with a lower (better) ODI score, but higher BMI and smoking were associated with worse ODI scores. See Table 19 for the full and final backward regression models for predicting ODI using patient characteristics (BMI,sex, age, smoking, employment status and depression).

Insurance types (commercial insurance, Medicare, Medicaid, worker's compensation and tricare) were evaluated for effect on ODI with multiple regression, in combination with the patient characteristics of BMI, smoking and employment status, which were significant in the first model. In the final model, higher BMI and smoking were associated with higher (worse) ODI scores, and having commercial insurance or Medicare were associated with lower (better) ODI scores ($F = 8.597$, $p. = .000$), explaining 18% of the variance. See Table 20 for the coefficients, significance and R^2 for the full and the final regression models for predicting ODI scores using patient characteristics (BMI, employment status and smoking) and insurance type.

Table 19
Coefficients and Observed Levels of Significance for the Full and Final Backward Regression Models for Predicting ODI Score Using Patient Characteristics (*N* = 162)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		Beta	Std. Error	Beta			
Full	(Constant)	31.921	8.082		3.950	.000	16.3
	BMI	.392	.171	.172	2.300	.023[b]	
	sex	1.140	2.959	.029	.385	.701	
	age	.073	.091	.064	.800	.425	
	smoking	13.198	3.397	.309	3.885	.000[c]	
	employment status	-5.013	3.035	-.129	-1.652	.101	
	depression	2.925	3.192	.071	.916	.361	
Final	(Constant)	36.975	5.607		6.594	.000	15.4
	BMI	.424	.168	.186	2.533	.012[b]	
	smoking	12.652	3.167	.297	3.995	.000[c]	
	employment status	-5.821	2.879	-.150	-2.022	.045[b]	

Dependent Variable = Oswestry Disability Index (ODI)
[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

Using backward multiple regression BMI, sex, age, smoking, employment status and depression were examined for their effect on SF-36 physical function subscale scores. BMI, age, employment status and depression were significant in the final model, explaining 17.7% of the variance (F = 8.399, *p*. = .000). BMI, depression and age were associated with lower (worse) physical function subscale scores, while being employed was associated with higher (better) physical function subscale scores. See Table 21 for the coefficients, significance and R^2 for the full and final backward regression models for predicting SF-36 physical function subscale scores using patient characteristics (BMI, sex, age, smoking, employment status and depression).

Table 20

Coefficients and Observed Levels of Significance for the Full and Final Multiple Regression Models for Predicting ODI Scores Using Patient Characteristics (BMI, Employment Status and Smoking) and Insurance Type (*N* = 162)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		Beta	Std. Error	Beta			
Full	(Constant)	49.142	8.345		5.889	.000	.193
	BMI	.307	.173	.134	1.776	.078[a]	
	smoking	9.689	3.467	.227	2.795	.006[b]	
	employment status	-4.146	3.391	-.107	-1.223	.223	
	workers compensation	-9.991	11.623	-.070	-.860	.391	
	commercial insurance	-10.623	5.964	-.274	-1.781	.077[a]	
	medicare	-10.508	6.468	-.222	-1.625	.106	
	tricare	-7.771	13.877	-.045	-.560	.576	
	medicaid	.319	6.691	.005	.048	.962	
Final	(Constant)	46.828	6.975		6.714	.000	.180
	BMI	.317	.170	.139	1.865	.064[a]	
	smoking	10.015	3.407	.235	2.940	.004[b]	
	commercial insurance	-11.429	3.809	-.294	-3.000	.003[b]	
	medicare	-8.889	4.664	-.188	-1.906	.058[a]	

Dependent Variable = Oswestry Disability Index (ODI)

[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

Table 21
Coefficients and Observed Levels of Significance for the Full and Final Backward Regression Models for Predicting SF-36 Physical Function Subscale Score Using Patient Characteristics (*N* = 161)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		Beta	Std. Error	Beta			
Full	(Constant)	54.119	4.784		11.312	.000	.196
	BMI	-.376	.101	-.274	-3.729	.000[c]	
	sex	-1.654	1.753	-.071	-.943	.347	
	age	-.157	.054	-.229	-2.908	.004[b]	
	smoking	-3.594	2.033	-.139	-1.768	.079[a]	
	depression	-2.846	1.892	-.114	-1.504	.135	
	employment status	2.901	1.791	.124	1.619	.107	
Final	(Constant)	50.299	4.351		11.559	.000	.177
	BMI	-.369	.101	-.269	-3.651	.000[c]	
	age	-.130	.052	-.189	-2.493	.014[b]	
	depression	-3.496	1.856	-.140	-1.884	.061[a]	
	employment status	3.727	1.744	.160	2.137	.034[b]	

Dependent Variable = SF-36 physical function subscale
[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

Insurance types (commercial insurance, Medicare, Medicaid, worker's compensation and tricare) were evaluated for effect on the physical function subscale of the SF-36 using multiple regression, in combination with the patient characteristics of BMI, age, employment status and depression. Since smoking was nearly significant in the first multiple regression, smoking was also added. In the final model, BMI, age, smoking and having Medicaid insurance were all associated with worse physical function subscale scores and explained 18.2% of the variance (F = 8.689, *p*. = .000). See Table 22 for the coefficients, significance and R^2 for the full and the

final regression models for predicting SF-36 physical function subscale scores using patient characteristics (BMI, depression, age, employment status and smoking) and insurance type.

Table 22
Coefficients and Observed Levels of Significance for the Full and Final Multiple Regression Models for Predicting SF-36 Physical Function Subscale Scores Using Patient Characteristics (BMI, Depression, Age, Employment Status and Smoking) and Insurance Type (*N* = 161)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		Beta	Std. Error	Beta			
Full	(Constant)	53.866	5.725		9.408	.000	.207
	BMI	-.342	.106	-.249	-3.243	.001[b]	
	age	-.201	.073	-.292	-2.757	.007[b]	
	smoking	-2.300	2.111	-.089	-1.089	.278	
	employment status	2.005	2.081	.086	.963	.337	
	depression	-2.648	1.900	-.106	-1.394	.166	
	commercial insurance	1.339	3.673	.057	.365	.716	
	medicare	1.925	4.581	.068	.420	.675	
	workers compensation	-1.955	7.015	-.023	-.279	.781	
	tricare	-5.003	8.394	-.048	-.596	.552	
	medicaid	-3.730	4.047	-.106	-.922	.358	
Final	(Constant)	55.603	4.286		12.972	.000	.182
	BMI	-.361	.102	-.263	-3.536	.001[b]	
	age	-.191	.052	-.278	-3.639	.000[c]	
	smoking	-3.456	1.994	-.134	-1.733	.085[a]	
	medicaid	-5.839	2.748	-.166	-2.125	.035[b]	

Dependent Variable = SF-36 physical function subscale
[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

The relationship between pain location and physical function.

One-way analysis of variance was used to determine if the presence of back pain and leg pain together was related to worse physical function consistent with the review of literature. The groups were: back pain only, back pain with leg pain, and leg pain only. There was a significant between groups difference (F = 3.582, *p*. = .030), indicating that the group means were different. To determine which means were significantly different, a multiple comparison test was used. The presence of back and leg pain together was associated with higher (worse) scores on the ODI, compared to back pain or leg pain alone, using Least Significant Difference (LSD) for multiple comparisons (*p*. = .025). See Table 23 for one-way analysis of variance for the between groups difference for pain location and ODI scores. Table 24 presents multiple comparisons correction for the between groups difference and ODI scores.

Table 23
One-way ANOVA for Between Groups Difference for Pain Location and ODI Scores (*N* = 162)

	Sum of Squares	df	Mean Square	F	Sign.
Between Groups	2486.399	2	1243.200	3.582	.030
Within Groups	54830.023	158	347.025		
Total	57316.422	160			

Dependent Variable: ODI Scores
df: degrees of freedom
Sign.: Significance
Groups: Back pain only, back pain and leg pain, leg pain only

Table 24
Multiple Comparison Test to Determine Which Means Differed for Pain Location and ODI Scores (*N* = 162)

Multiple Comparison Test	Pain Location	Pain Location	Sign.	95% Confidence Interval	
				Lower Bound	Upper Bound
Least Significant Difference	back pain only	back and leg pain	.058	-13.67	.22
		leg pain only	.524	-6.64	12.99
	back and leg pain	back pain only	.058	-.22	13.67
		leg pain only	.025[a]	1.23	18.56
	leg pain only	back pain only	.524	-12.99	6.64
		back and leg pain	.025[a]	-18.56	-1.23

Dependent Variable: ODI Scores
[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

In contrast, there was no association between location of pain and physical function subscale scores from the SF-36. There was no significant between groups difference between pain location (back pain only, back pain and leg pain, leg pain only) and physical function subscale scores (F = 1.503, *p*. = .226). See Table 25 for one-way ANOVA for between groups difference for pain location and SF-36 physical function subscale scores.

There were physiological and situational factors that were found to contribute to symptoms and physical function in this study. The physiological factor smoking contributed to higher pain VAS. The situational factor Medicaid insurance also contributed to higher pain VAS. There were no physiological, situational or psychological factors that contributed to the symptoms of numbness or weakness. The physiological factors of higher BMI and smoking contributed to worse scores for physical function on both the ODI and the physical function subscale of the SF-36. The situational factors of having Medicare and Commercial insurance were associated with better physical function scores on the ODI. These findings are consistent

with previous findings that smoking is associated with worse low back pain, although the mechanism is unclear (Karahan, Kav, Abbasoglu & Dogan, 2009; Shiri, Karppinen, Lein-Arjas, Solovieva, & Viikari-Juntura, 2010). Medicaid insurance has been associated with worse health outcomes in general, and the key factor may be reduced or restricted coverage for treatments that reduce pain, such as physical therapy and spinal injections (Greenstein, Moskowitz, Gelijns & Egorova, 2012; Kruper, et al., 2011; McClelland, Guo & Okuyemi, 2011; Yorio, Yan, Xie & Gerber, 2012). BMI and smoking were associated with worse physical function scores, and this may be related to restricted pulmonary function and decreased mobility related to weight. These findings are consistent with previous findings (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn et al, 2013).

Table 25

One-way ANOVA for Between Groups Difference for Pain Location and SF-36 Physical Function Subscale Scores (*N* = 161)

	Sum of Squares	df	Mean Square	F	Sign.
Between Groups	398.184	2	199.092	1.503	.226
Within Groups	20801.534	157	132.494		
Total	21199.718	159			

Dependent Variable: SF-36 physical function subscale scores
df: degrees of freedom
F: F-statistic
Groups: Back pain only, back pain and leg pain, leg pain only

Aim 2 Analysis

For Aim 2, to develop a predictive model for the outcome of physical function in persons receiving non-surgical interventions for lumbar degenerative conditions using symptoms (back and/or leg pain, pain VAS, numbness, and weakness) and physiological, situational, and

psychological patient factors, general linear modeling was used. Using the significant predictors for ODI score from the Aim 1 analysis (smoking and BMI), these were added into an analysis of variance with symptoms. Weakness and pain location were not significant and were dropped from the model. With general linear modeling, BMI, pain VAS, smoking and extremity numbness were kept in the final model. These variables were entered into a backward step-wise multiple regression with ODI score the dependent variable. BMI, smoking, pain VAS and extremity numbness were significantly associated with ODI scores (F = 20.679, *p*. = .000) and explained almost 35% of the variance. See Table 26 for coefficients, observed level of significance and R^2 for the final backward step-wise multiple regression for predicting ODI scores using patient characteristics (BMI, smoking, pain VAS) and symptoms (extremity numbness).

Similar findings were supported for physical function subscale scores. Once again, using the significant predictors for SF-36 physical function scores from the Aim 1 analysis, (BMI, age and smoking) were added with symptoms into an analysis of variance. With general linear modeling, BMI, age and pain VAS were kept in the final model. These variables were entered into a backwards step-wise multiple regression with SF-36 physical function subscale score the dependent variable. BMI, age and pain VAS were significantly negatively associated with physical function subscale scores (F = 18.019, *p*. = .000), explaining almost 26% of the variance. See Table 27 for coefficients, observed level of significance and R^2 for the full and the final backward step-wise multiple regression for predicting SF-36 physical function subscale scores using patient characteristics (BMI and age) and symptoms (pain VAS).

Table 26
Coefficients and Observed Level of Significance for the Final Backward Step-wise Multiple Regression for Predicting ODI Scores Using Patient Characteristics (BMI, Smoking, Pain VAS and Symptoms (Extremity Numbness) (*N* = 162)

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	Sign.	R^2
		B	Std. Error	Beta			
Final	(Constant)	10.153	5.795		1.752	.082	.347
	BMI	.279	.146	.125	1.907	.058[a]	
	smoking	6.818	2.853	.163	2.390	.018[b]	
	Pain VAS	4.196	.607	.472	6.912	.000[c]	
	extremity numbness	4.992	2.516	.129	1.984	.049[b]	

Dependent variable: ODI scores
[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

There were physiological and situational factors with symptoms that had predictive value for physical function in this study. Higher BMI, smoking, higher pain VAS and extremity numbness explained 35% of the variance in ODI scores, while higher BMI, older age and higher pain VAS explained 26% of the variance in SF-36 physical function subscale scores.

Table 27
Coefficients and Observed Level of Significance for the Full and Final Backward Step-wise Multiple Regression for Predicting SF-36 Physical Function Subscale Scores Using Patient Characteristics (BMI and Age) and Symptoms (Pain VAS)
(*N* = 161)

Model		Unstandardized Coefficients		Standardized Coefficients			
		B	Std. Error	Beta	*t*	Sign.	R^2
Full	(Constant)	64.600	4.554		14.184	.000	.261
	BMI	-.347	.095	-.255	-3.657	.000[c]	
	smoking	-1.646	1.916	-.064	-.859	.391	
	pain VAS	-1.857	.392	-.344	-4.734	.000[c]	
	age	-.155	.049	-.227	-3.161	.002[b]	
Final	(Constant)	64.010	4.499		14.229	.000	.257
	BMI	-.341	.095	-.251	-3.606	.000[c]	
	pain VAS	-1.953	.375	-.362	-5.202	.000[c]	
	age	-.144	.047	-.210	-3.045	.003[b]	

Dependent Variable: SF-36 physical function subscale score
[a] indicates p-values < 0.10, [b] indicates p-values < 0.05, [c] indicates p-values < 0.001

Summary of Findings for Aims 1 and 2

There were patient physiological and situational characteristics with significant associations with symptoms. Specifically, smoking, having Medicaid insurance, or not having insurance was significantly associated with higher pain VAS ratings.

There were patient physiological and situational characteristics that were also associated with physical function. Specifically, higher BMI and smoking, along with older age and having Medicaid insurance were all significantly associated with worse SF-36 physical function subscale scores. Higher BMI and smoking were associated with worse ODI scores, while having Medicare or Commercial insurance were associated with better ODI scores. With older age, physical function may be declining and degenerative spinal changes increase over time (Cheung, et al., 2009).

There were patient physiological and situational characteristics that, along with symptoms, were able to explain a portion of the variance in physical function scores. In particular, higher BMI, smoking, higher pain VAS and numbness accounted for 35% of the variance in ODI scores. Higher BMI, older age and higher pain VAS accounted for 26% of the variance in SF-36 physical function subscale scores.

Aim 3 Study Subjects

To select study subjects for Aim 3, the study population of 163 randomly selected medical records with complete patient characteristics, symptom and outcome measures entered on an excel sheet were subjected to computerized randomization. Working from the beginning of the list after randomization, individuals were contacted by telephone. One hundred five individuals were called before 30 agreed to provide saliva samples, representing 29% of individuals called. The main reason for the small percentage of consenting subjects was inability to contact individuals by phone. For many, the phone number had been disconnected. For a few subjects, transportation was a barrier. One subject arrived, but could not find parking and left without being tested. One subject could not find child care. Each time a subject cancelled or failed to show for saliva collection, another subject was contacted. At the end of a two-week period of saliva collection, 2 subjects cancelled, leaving a total of 28 saliva samples collected. The reduction of desired study subjects in Aim 3 was approved by the investigator's Dissertation Committee.

Demographics and Patient Characteristics for Genotyped Subjects

The mean BMI for the genotyped subjects was similar to the mean study population BMI at 30.01. There was no statistically significant difference in the BMI of the study population and the genotyped subjects using *t*-test ($p. = .766$). Males comprised 53.6% ($n = 15$) of the

genotyped subjects. The average age of genotyped subjects was 53.36 (S.D. = 15.2), not statistically different from the study population as a whole (*p*. = .806). Ninety-three percent (*n* = 26) of the genotyped subjects were non-smokers compared to 71.8% of the study sample subjects and this was significantly statistically different (x^2 = 7.415; *p*. = .006). Similar to the study population, 57% (*n* = 16) of the genotyped subjects was working. This was not statistically different from the study population as a whole (x^2 = 2.538; *p*. = .143). Among the genotyped subjects, 68% (*n* = 19) were covered by commercial insurance, 18% (*n* = 5) had Medicare, 7% (*n* = 2) had Medicaid, 3.5% (*n* = 1) had worker's compensation, and 3.5% (*n* =1) had no insurance. See Table 28 for genotyped subjects, *N* and % for categorical variables.

Eighteen percent (*n* = 5) of genotyped subjects had been diagnosed with depression (by review of the medical record) compared to 31.3% of the study population, but this was not statistically different (*p*. = .118). The mean pain VAS among the genotyped subjects was 6.34 compared to the mean pain VAS of 6.83 for the study sample (S.D. = 1.96), not a statistically significant difference (*p*. = .200). See Table 28 for genotyped subjects, *N* and % for categorical variables. See Table 29 for genotyped subjects patient characteristics, range, minimum, maximum, mean and SD for continuous variables. See Table 30 for genotyped subjects' pain VAS mean, maximum, minimum.

Table 28
Genotyped Subjects Patient Characteristics, *N* and % for Categorical Variables (*N* = 28)

Category	Characteristic	Variable	*N*	%
Physiological	Smoking	Non-smoking	26	93
		Smoking	2	7
	Sex	Female	13	46.4
		Male	15	53.6
Situational	Work Status	Working	16	57
		Non-working	12	43
	Insurance Type	Commercial	19	68
		Medicare	5	18
		Medicaid	2	7
		Auto		
		Worker's Compensation	1	3.5
		No Insurance	1	3.5
Psychological	Depression	Depressed (per medical record)	5	18
		Not Depressed	23	82

Table 29
Genotyped Subjects Patient Characteristics, Range, Minimum, Maximum, Mean and SD for Continuous Variables (*N* = 28)

Category	Characteristic	Range	Sample Mean	SD
Physiological	BMI	20.68-71.04	30.01	9.75
	Age	22-80	53.6	15.239

Table 30
Genotyped Subjects Symptom Continuous Variable: Pain VAS (*N* = 28)

Symptom	Range	Mean	SD
Pain VAS for Genotyped Subjects	1.5-10	6.34	1.963

Outcome Measures for the Genotyped Subjects

The ODI score was missing for one of the genotyped subjects. The mean ODI score for the genotyped subjects was 45.56 (S.D. = 17.88). The mean physical function subscale score for the genotyped subjects was 35.76 (S.D. = 11.05), and the mean mental health subscale score for the genotyped subjects was 52.52 (S.D. = 19.47). There was no statistically significant difference between the study population and the genotyped subjects for ODI and PF scores (*p*. = .111 and *p*. = .096, respectively). However, the difference between mental health subscale scores between the two populations was statistically significant (*p*. = .001). Thus, the mental health scores were significantly better for the genotyped subjects than for the study population as a whole. The study population mean mental health subscale score was 44.73 and published health population norm score is 53.43. See Table 31 for physical function outcome scores for the ODI and the SF-36 for the genotyped subjects.

Table 31
Genotyped Subjects Physical Function Scores: Range, Minimum, Maximum, Mean and SD (*N* = 28)

Outcome Measure	*N*	Range	Mean	SD
ODI	27	4-74	45.56	17.85
SF-36 Physical Function Subscale	28	14.94-57.03	35.76	11.05

In summary, the genotyped subjects did not differ significantly in the areas of BMI, sex, age and employment status. Fewer genotyped subjects smoked and fewer were depressed than in the study population. The mean pain VAS was slightly lower in the genotyped subjects, but this was not statistically significant. The insurance types were slightly differently represented among the genotyped subjects, with slightly more subjects with commercial insurance than in the study sample.

Although the genotyped subjects had slightly better ODI scores than the study population as a whole, this was not statistically significant. Physical function subscale scores were similar, but this was not statistically significant. The genotyped subjects had statistically significantly better mental health subscale scores than the study population as a whole.

Genotyping Results

Genotyping was performed by staff at the Core Genomics Lab at Michigan State University. The 28 saliva samples were tested for *COL9A2* (rs2228564), *COL9A3* (rs61734651), *OPRM1* (rs1799971), *COMT* (rs4680), *VDR* (rs*731236*) and for VNTR for *ACAN*. All 28 saliva samples yielded valid testing results for the genes being tested, with the exception of *ACAN*. Two saliva samples did not amplify for *ACAN* VNTR testing, and were not able to be successfully genotyped, leaving 26 valid results for *ACAN*.

The genotyping results for *COL9A2* revealed that 19 out of 28 individuals were homozygous for the A/A allele, 8 were heterozygotes with the A/G allele, and one was homozygous for the G/G allele. Therefore, 9 subjects possessed the Trp2 */G allele associated with a higher rate of disc degeneration. The genotyping results for *COL9A3* revealed limited diversity, with 27 of the subjects homozygous for the C/C allele, and one heterozygous C/T subject. Therefore, one subject possessed the Trp3 */T allele associated with a higher rate of disc degeneration. Testing for *OPRM1* revealed little diversity as well, with 24 subjects homozygous for the A/A allele, one homozygous for the G/G allele, and three heterozygotes. Results for *COMT* revealed greater diversity in genotype, with 12 A/A homozygotes, 5 G/G homozygotes and 11 heterozygotes. Fourteen subjects were heterozygous C/T for *VDR*, 13 were homozyogous T/T, and one was homozygous C/C.

The VNTRs for *ACAN* varied from 24 to 30 repeats, with seven different alleles identified. In addition, seven different genotypes were identified, including 24/27, 27/29, 28/28, 28/30, 29/29, 30/30 and 30/33. Most subjects were homozygous, but four subjects were heterozygous for *ACAN* VNTR. In summary, there was very little diversity represented in the *COL9A3*, *OPRM1* and *ACAN* genotypes. The other genes tested exhibited greater diversity in genotype. Diversity in genotype has been shown to vary by ethnic group. However, the small sample size of genotyped subjects did not allow for sufficient data to compare study genotype representation with known populations. Also, the ethnicity of study subjects was not explored in this study.

Aim 3 Analysis

For Aim 3, to explore the impact of the physiological factor genotype on symptoms, first the genotypes for *COL9A2*, *COL9A3*, *OPRM1*, *COMT*, *VDR* and *ACAN* VNTR from the 28

subjects with saliva samples were each analyzed for their effects on symptoms. Next, the relationship between genotype and outcome measures was examined.

Relationship between genotype and symptoms.

Genotypes *COL9A2*, *COL9A3*, *OPRM1*, *COMT* and *VDR* were examined for their effects on pain VAS using one-way analysis of variance. None of the genotypes were found to have a significant effect on pain VAS. However, *OPRM1* exhibited a trend toward higher pain VAS in individuals who were A/A, with lower pain scores for those A/G, and the lowest scores for G/G individuals, although this was not statistically significant (*p*. = .201). When analyzed as a dichotomous variable, *OPRM1* continued the trend toward a significant association with pain VAS, but was still not statistically significant (*p*. = .108). See Table 32 for analysis of variance results of the genotypes *COL9A2*, *COL9A3*, *OPRM1*, *COMT* and *VDR* with pain VAS.

A scatter plot to determine any trends in the relationship between *ACAN* VNTR alleles and pain VAS was analyzed. There was no observable linear trend between *ACAN* VNTR alleles and pain VAS. There was no significant correlation between *ACAN* VNTR alleles and pain VAS (r^2 = -.047, *p*. = .821).

To explore the relationship between genotype and pain location, chi-square tests were used for *COL9A2*, *COL9A3*, *OPRM1*, *COMT*, *VDR* and *ACAN* VNTR alleles and back pain, back pain and leg pain and leg pain only. There was insufficient evidence to conclude that there was a relationship between genotypes *COL9A2*, *COL9A3*, *OPRM1*, *COMT*, *VDR* and *ACAN* VNTR alleles and pain location.

Table 32

One-way ANOVA for Between Groups Difference (Genotypes) *COL9A2, COL9A3, OPRM1, COMT* and *VDR* and Pain VAS (*N* = 28)

Genotype		Sum of Squares	df	Mean Square	F	Sign.
COL9A2 rs2228564	Between Groups	6.704	2	3.352	.861	.435
	Within Groups	97.322	25	3.893		
	Total	104.027	27			
COL9A3 rs61734651	Between Groups	.453	1	.453	.114	.739
	Within Groups	103.574	26	3.984		
	Total	104.027	27			
OPRM1 rs1799971	Between Groups	12.527	2	6.263	1.711	.201
	Within Groups	91.500	25	3.660		
	Total	104.027	27			
COMT rs4680	Between Groups	10.274	2	5.137	1.370	.273
	Within Groups	93.753	25	3.750		
	Total	104.027	27			
VDR rs731236	Between Groups	9.791	2	4.895	1.299	.291
	Within Groups	94.236	25	3.769		
	Total	104.027	27			
OPRM1 rs1799971 Dichotomous A/A, */G	Between Groups	10.026	1	10.006	2.767	.108
	Within Groups	94.021	26	3.616		
	Total	104.027	27			

Dependent Variable: Pain VAS
df: Degrees of Freedom
Sign: Significance
COL9A2 Groups: A/A, A/G, G/G
COL9A3 Groups: C/C, C/T
OPRM1 Groups: A/A, A/G, G/G
COMT Groups: A/A, A/G, G/G
VDR Groups: C/C, C/T. T/T

Because of the lack of diversity represented in the genotypes *COL9A2* and *OPRM1*, these genotypes were also tested with pain location as dichotomous variables (A/A and */G). There was insufficient evidence to conclude that there was a relationship between *COL9A2* and *OPRM1* and pain location, testing these genotypes as dichotomous variables. See Table 33 for chi-square tests for relationships between genotype and pain location (back pain only, back pain and leg pain, leg pain only). Similarly, using chi-square testing, there were no statistically significant relationships between genotypes and the symptoms of numbness and weakness.

Table 33
Chi-square Tests for Genotype as Predictors of Pain Location (Back Pain Only, Back Pain and Leg Pain, Leg Pain Only) (*N* = 28)

Genotype	Chi-square	df	Sign.
COL9A2 rs2228564	2.574	4	.631
COL9A3 rs61734651	.899	2	.638
OPRM1 rs1799971	5.279	4	.260
COMT rs4680	2.133	4	.711
VDR rs731236	4.335	4	.363
ACAN VNTR alleles	17.011	12	.149
COL9A2 rs2228564 Dichotomous (AA/*G)	1.981	2	.371
OPRM1 rs1799971 Dichotomous (AA/*G)	1.254	2	.534

Dependent Variable: Pain location (Back pain only, back pain and leg pain, leg pain only)
df: Degrees of Freedom
Sign.: Significance
ACAN VNTR alleles: 24/27, 27/29, 28/28, 28/30, 29/29, 30/30, 30/33

Relationship between genotype and outcome measures.

Because there were two outcome measures, the ODI and the physical function subscale from the SF-36, separate statistical tests were used to explore the influence of patient genotype on physical function. These tests will be reported separately.

First the genotypes *COL9A2*, *COL9A3*, *OPRM1*, *COMT* and *VDR* were analyzed using one-way analysis of variance with ODI scores. *COL9A2*, *COL9A3*, *COMT* and *VDR* genotypes were not significantly associated with ODI scores. *OPRM1* genotype was significantly associated with ODI scores. A/A *OPRM1* genotype was associated with higher (worse) ODI scores ($F = 3.643$, $p. = .042$). See Table 34 for one-way analysis of variance for genotype and ODI scores.

A correlation was computed to test the relationship between *ACAN* VNTR alleles and ODI scores. There was no significant correlation between *ACAN* VNTR alleles and ODI scores ($r^2 = -.007$, $p. = .974$). No significant linear trend between *ACAN* VNTR allele and ODI scores was identified on a scatter plot.

Finally, the genotypes *COL9A2*, *COL9A3*, *OPRM1*, *COMT* and *VDR* were analyzed using one-way analysis of variance with SF-36 physical function subscale scores. There were no genotypes that were significantly associated with SF-36 physical function subscale scores. Because of the lack of diversity represented in the genotype *OPRM1*, this genotype was also tested as a dichotomous variable (A/A and */G) with SF-36 physical function subscale score. Treated as a dichotomous variable, *OPRM1* was significantly associated with SF-36 physical function subscale scores, with A/A genotypes associated with lower (worse) physical function scores ($F = 4.511$, $p. = .043$), similar to the findings with ODI scores. See Table 35 for one-way analysis of variance for genotypes and SF-36 physical function subscale scores.

Table 34
One-way ANOVA for Between Groups Difference (Genotypes) *COL9A2, COL9A3, OPRM1, COMT* and *VDR* and ODI Scores (*N* = 27)

Genotype		Sum of Squares	df	Mean Square	F	Sign.
COL9A2 rs2228564	Between Groups	223.167	2	111.583	.332	.721
	Within Groups	8059.500	24	335.813		
	Total	8282.667	26			
COL9A3 rs61734651	Between Groups	32.051	1	32.051	.097	.758
	Within Groups	8250.615	25	330.025		
	Total	8282.667	26			
OPRM1 rs1799971	Between Groups	1929.043	2	964.522	3.643	.042
	Within Groups	6353.623	24	264.734		
	Total	8282.667	26			
COMT rs4680	Between Groups	584.800	2	292.400	.912	.415
	Within Groups	7697.867	24	320.744		
	Total	8282.667	26			
VDR rs731236	Between Groups	367.590	2	183.795	.557	.580
	Within Groups	7915.077	24	329.795		
	Total	8282.667	26			

Dependent Variable: ODI scores
df: Degrees of Freedom
Sign.: Significance
COL9A2 Groups: A/A, A/G, G/G
COL9A3 Groups: C/C, C/T
OPRM1 Groups: A/A, A/G, G/G
COMT Groups: A/A, A/G, G/G
VDR Groups: C/C, C/T. T/T

A correlation was computed to test the relationship between *ACAN* VNTR alleles and SF-36 physical function subscale scores. There was no significant correlation between *ACAN* VNTR alleles and SF-36 physical function subscale scores ($r^2 = .104, p. = .613$). A scatter plot

did not reveal a linear relationship between *ACAN* VNTR alleles and SF-36 physical function subscale scores.

In summary, there were no significant relationships identified between the genotypes of the 28 subjects from Exploratory Aim 3 and symptoms, although there was a trend toward a significant relationship between OPRM1 genotype and pain VAS. OPRM1 genotype was found to have a significant relationship with ODI scores, and when treated as a dichotomous variable (A/A and */G), *OPRM1* was significantly associated with SF-36 physical function subscale scores. Since the genotyped sample was exploratory, a small sample size was used. Although the only significant finding was the association between OPRM1 and pain VAS, it would be premature to dismiss potential associations with the other genotypes, because of the small sample size used. A discussion of these results will be found in Chapter VI.

Table 35

One-way ANOVA for Between Groups Difference (Genotypes) *COL9A2, COL9A3, OPRM1, COMT* and *VDR* and SF-36 Physical Function Subscale Scores (*N* = 28)

Genotype		Sum of Squares	df	Mean Square	F	Sign.
COL9A2 rs2228564	Between Groups	188.550	2	94.275	.758	.479
	Within Groups	3109.511	25	124.380		
	Total	3298.062	27			
COL9A3 rs61734651	Between Groups	77.475	1	77.475	.625	.436
	Within Groups	3220.586	26	123.869		
	Total	3298.062	27			
OPRM1 rs1799971	Between Groups	487.963	2	243.982	2.171	.135
	Within Groups	2810.098	25	112.404		
	Total	3298.062	27			
COMT rs4680	Between Groups	97.990	2	48.995	.383	.686
	Within Groups	3200.071	25	128.003		
	Total	3298.062	27			
VDR rs731236	Between Groups	416.883	2	208.441	1.809	.185
	Within Groups	2881.179	25	115.247		
	Total	3298.062	27			
OPRM1 rs1799971 Dichotomous (A/A, */G)	Between Groups	487.594	1	487.594	4.511	.043
	Within Groups	2810.468	26	108.095		
	Total	3298.062	27			

Dependent Variable: SF-36 Physical Function Subscale Scores
df: Degrees of Freedom
Sign.: Significance
COL9A2 Groups: A/A, A/G, G/G
COL9A3 Groups: C/C, C/T
OPRM1 Groups: A/A, A/G, G/G
COMT Groups: A/A, A/G, G/G
VDR Groups: C/C, C/T. T/T
OPRM1 Dichotomous Groups: A/A, */G

CHAPTER VI

Discussion and Implications

The focus of this study was on patient physiological, situational and psychological characteristics and symptoms, and their combined effects on physical function for persons with lumbar degenerative conditions. A discussion of the results with interpretation and how they support or differ from existing research and limitations of this study will be presented in this chapter by Aims. Last, this final chapter will present contribution to science and implications for nursing practice, research, and policy.

Discussion of Sample Patient Characteristics

The sample patient characteristics included BMI, sex, age, smoking, employment status, worker's compensation claim, insurance type and depression. The symptoms studied included pain VAS, pain location (low back pain only, leg pain only and back and leg pain combined), extremity weakness and extremity numbness. Outcome measures included scores on the ODI and the physical function subscale of the SF-36. Additionally, mental health subscale scores from the SF-36 were also examined, to compare the study population to population norm scores. All patient data except genotype was obtained from the medical records randomly chosen from a database of patients seeking care from the spine service from 2009-2012. Genotype data was obtained from a randomly selected subset of this study population in February, 2014.

Discussion of Sample Physiological Characteristics.

The mean BMI of the sample was 30.44 (S.D. = 8.41), considered obese (National Institutes of Health, 2014). In fact, nearly 30% (n = 48) of subjects in the sample were overweight, nearly 30% (n = 48) were considered obese and over 12% (n = 20) were considered class III obese. Nearly 42% (n = 116) of the entire sample had a BMI of 30 or greater, compared

to the state of Michigan average obesity rate of 31.1% in 2012 (CDC, 2014). The study population was therefore heavier than the Michigan average.

Fifty-eight percent (n = 91) of the sample was women. There were 72 men (n = 42) in the sample. Males and females were approximately equally represented in the study. The sample mean age was 54 (S.D. = 16.85). Seventy-three percent (n = 119) were younger than 65. The age range of the sample was 22-93.

More than 28% (n = 46) of the sample smoked. Thirty-five percent (n = 24) of men were smokers, while 23% (n = 22) of the women smoked. This compares to the smoking rate of American adults, which is 18.1% (CDC, 2014). Among American adult males, 20.5% are smokers. Among American adult women, 15.8% are smokers. Thus, the sample smoking rate was higher than the American average rates for adults, both men and women.

Discussion of Sample Situational Characteristics.

More than half of the study subjects were not working at the time of their presentation to the spine service (56%, n = 92). Among men, 52% (36) were not working. Sixty percent of women were not working (56). And, among those 119 subjects of working age (less than 65), 46% (55) were not working. It is undetermined whether work status in this population was directly related to a spinal cause.

Only 3 individuals from the sample had worker's compensation claims and all three subjects with worker's compensation claims were not working. This represented only 1.84% of the sample, thus making it difficult to make conclusions regarding its influence on symptoms and physical function in Aim 1. Additionally, because of the small proportion of the sample with worker's compensation, this variable did not play a significant role in the predictive modeling of Aim 2.

The majority of the sample (n = 147, approximately 90%) was covered by three types of insurance plans: commercial, Medicare and Medicaid. Commercial insurance covered 57% (93) of the sample, followed by Medicare (20.9%, or 34 subjects). Twenty subjects (12.3 %) had Medicaid insurance, and 8 subjects (4.9%) had no insurance. Three subjects (1.8%) had worker's compensation, 3 subjects (1.8%) had auto insurance, and two (1.2%) had tricare, an insurance plan for those in the armed service. As would be expected, of those working, the percentage of those covered by commercial insurance rose to 87%, (n = 62) with 4% (n = 3) covered by Medicare, 4% (n = 3) covered by Medicaid, 3% (n = 2) with no insurance and 1 person with auto insurance. Most subjects were covered by some form of insurance. Given the nature of the clinical condition of this population (low back pain), the low proportion of subjects covered by worker's compensation was unexpected.

Discussion of Sample Psychological Characteristic.

More than 31% (n = 51) of the sample had a clinical diagnosis of depression obtained from review of the medical record received from the referring physician at the time of the first visit to the spine service. More women (38%, n = 36) were diagnosed with depression than men (22%, n = 15), a difference that was statistically significant. SF-36 mental health subscale scores and the diagnosis of depression were related (t-statistic = 4.180, p. = .000; Mann-Whitney U test p. = .000). And, SF-36 mental health subscale scores were significantly lower for those with the diagnosis of depression. The mean sample mental health score was 44.73 (S.D. = 14.4), lower than healthy population norm score (53.43 S.D. = 8.38) (Ware et al., 2007). The sample mean mental health subscale score was higher than the published mean score for those with depression, which is 36.7 (S.D. = 11.08) (Ware et al., 2007). Thus, the sample mean mental health was worse than a healthy population, but not as low as scores for a population with depression. It is

possible that the study sample possessed more associated factors that may have impacted mental health subscale scores. These factors may include the higher rates of smoking, more severe estimations of pain, and higher rates of obesity than average. Medical co-morbidities were not explored in this study, and it is possible that the burden of medical co-morbidities could have contributed to depression in the subjects in this study.

In summary, the sample (n = 163) consisted of proportionately more obese individuals than the state of Michigan average. Slightly more females than males were represented in the sample. The age range of subjects in the sample was 22-93, with a mean age of 54 (S.D. = 16.85). The majority of subjects were younger than 65 (73%, n = 119). There were proportionately more smokers in the sample than the American average. This was true for both men and women.

Even though the majority of subjects in the sample were younger than 65 (n = 119), the majority of subjects were not working (56%, n = 92). In fact, of those who were younger than 65 (n = 119), 46% (n = 55) were not working. Only 3 of the 163 subjects were covered by worker's compensation, which made it difficult to fully assess the influence this type of insurance had on symptoms and physical function. By far, the most common insurance for the sample was commercial, followed by Medicare and Medicaid. There were more subjects without insurance than there were subjects with worker's compensation, auto, or tricare.

Nearly one third of the sample had a diagnosis of depression obtained from review of the medical record. There were more depressed females than depressed males. The sample mean SF-36 mental health subscale score was lower than a healthy population norm score, but not as low as the mean score for those with depression (Ware et al., 2007). Thus, the sample mean mental health was worse than a healthy population. SF-36 mental health subscale scores were

significantly related to the diagnosis of depression, helping to strengthen the validity of this variable.

Discussion of Symptoms of Sample

The mean pain VAS for the sample was 6.83 on a 0-10 scale (S.D. = 2.2). Males and females were similar with regard to pain VAS, with males reporting a mean pain VAS of 6.79 (S.D. = 2.46) and females reporting a mean pain VAS of 6.85 (S.D. = 1.99), a difference that was not statistically significantly different. Thus, the mean pain VAS for the sample approached severe pain, according to cut points identified by Jensen, Smith, Ehde & Robinsin, (2001), Kathy, Harris, Hadi and Chow (2007), and Serlin, Mendoza, Nakamura, Edwards and Cleeland, (1995). It is possible that the associated factors in this population, such as higher than average BMI, higher than average smoking rates and worse than average estimation of mental health may play a role in the subjects' estimation of pain. Pain treatments for the subjects were not known, and were beyond the scope of this study.

Twenty-seven subjects reported weakness (16.6%). Sixty-five subjects reported numbness (40%). One hundred subjects (60%) reported back pain and leg pain. Thirty-nine subjects (24%) reported back pain only. Twenty-three subjects (14%) reported leg pain only. Subjective numbness was reported by more subjects than weakness.

More subjects reported back and leg pain together than those reporting either pain location alone. There are studies that have examined the pain diagrams of subjects with specific pathologies (lumbar radiculopathy, sacro-iliac joint pain and facet joint pain). However, this study included all individuals who presented to the spine service for care, regardless of the specific anatomic diagnosis. The presence of back and leg pain together was associated with worse physical function than back pain alone or leg pain alone, consistent with previous findings

(Kongstead, Kent, Albert, Jensen & Manniche, 2012). Future studies should explore further the associations between pain location and physical function. This will be discussed in the Implications for Research section.

Discussion of Sample Outcome Measures

For ODI scores, higher values reflect worse physical function. The sample mean ODI subscale score was 50.96 (S.D. = 19.3) (range 0-90). Scores of 40-60 are associated with severe disability (Fairbank, Couper, Davies & O'Brien, 1980). Published norm scores for individuals with spinal metastases is 48.04 (Roland & Fairbank, 2000). Thus, the sample mean scores reflect worse physical function than scores associated with spinal metastases. This was an unexpected finding, and may be related to the other factors associated with physical function in this study, including BMI, smoking, pain VAS and numbness.

For SF-36 subscales, higher scores reflect better physical function. The mean SF-36 physical function subscale score for the sample was 32.57 (S.D. = 11.98, range: 14.94-57.03). Published healthy population norm score is 54.76 (S.D. = 6.04) (Ware et al., 2007). For comparison, published mean score for individuals with back pain and sciatica is 46.78 (S.D. = 11.14) and mean scores for individuals in the 25th percentile with back pain and sciatica is 40.87 (S.D. = 11.14). The sample mean SF-36 physical function subscale score was worse than mean scores for those with diabetes (42.52, S.D. = 11.18) and was only slightly better than scores for individuals in the 25th percentile with cancer (30.64, S.D. = 11.52) (Ware et al., 2007).

In summary, the physical function scores from both the ODI and the SF-36 physical function subscale indicate the sample was experiencing significant reduction in physical function. Moreover, the ODI scores were lower than for those in the 25th percentile for those

with similar lumbar diagnoses, and only minimally better than those with cancer, a condition with more serious health implications. Given the similarity of underlying diagnoses with those populations from whom the norm scores were obtained, the explanation for worse physical function scores in the study population is unclear. It is possible that the study population was overall more obese, had a higher rate of smoking and higher subjective ratings of pain that affected physical function scores than the populations used to determine the SF-36 population norm scores for lumbar pathologies. Co-morbidities were not examined in this study, but may have been a factor in the subjects' estimations of physical function.

Discussion of Results for Specific Aim 1

The purpose of Specific Aim 1 was to determine the contribution of physiological (BMI, sex, age, smoking status), situational (employment status, worker's compensation claim, insurance type), and psychological (depression) factors in persons with degenerative lumbar conditions to symptoms and physical function. First, the relationship between patient characteristics and symptoms will be examined. Next, the associations between patient characteristics and physical function will be reviewed.

Discussion of Associations between Patient Characteristics and Symptoms.

Multiple regression was used to explore the relationship between BMI, sex, age, smoking status, employment status and depression and pain VAS. Smoking was the only significant predictor of pain VAS, explaining 8.6% of the variance. That is, smoking was weakly associated with worse pain VAS scores, but more than 90% of the variance in pain VAS was not explained by the variables BMI, sex, age, smoking, employment status and depression. Since BMI and employment status were the last variables to be eliminated in the first regression, they were kept in the multiple regression model while insurance types were added to determine the effects on

pain VAS. In the final multiple regression model, smoking, having Medicaid insurance, or not having insurance were associated with worse pain VAS, explaining 13% of the variance in pain VAS scores. That is, smoking, having Medicaid insurance, or not having insurance were associated with worse pain VAS scores, leaving 87% of the variance unexplained by BMI, employment status, smoking, and insurance type. Thus, the variables included in the regression were not sufficient to explain a large portion of the variance, or, the sample may not have been large enough. The finding that smoking is related to pain is consistent with previous findings that associate smoking with higher levels of back pain, but the mechanism behind this is unclear (Karahan, Kav, Abbasoglu & Dogan, 2009; Shiri, Karppinen, Lein-Arjas, Solovieva, & Viikari-Juntura, 2010). And the associations between Medicaid insurance or not having insurance and pain VAS are consistent with previous findings that lack of insurance or under-funded insurance are associated with worse health outcomes in general (Greenstein, Moskowitz, Gelijns & Egorova, 2012; Kruper, et al., 2011; McClelland, Guo & Okuyemi, 2011; Yorio, Yan, Xie & Gerber, 2012). This finding may be due to a restricted number of physical therapy visits offered by Medicaid insurance. At the time these data were collected, local county Medicaid plans also required attendance at a 6 hour class on pain before spine injections were authorized, which served as a deterrent for some subjects in obtaining this treatment.

Next, the relationship between patient characteristics and the symptoms of numbness and weakness was tested. While age was the only significant variable in the final logistic regression model for weakness, it had no discriminatory value. And while employment status was the only significant variable in the final logistic regression model for numbness, it also had no discriminatory value. Therefore, it was concluded that BMI, sex, age, smoking, employment status and depression had no influence on the symptoms of numbness or weakness. It is likely

that these patient characteristic variables are not related to the symptoms of numbness and weakness.

Since pain location was a categorical variable, discriminant analysis was used to determine if patient characteristics (BMI, sex, age, smoking, employment status and depression) could predict pain location (back pain only, back and leg pain, leg pain only). Age and smoking were significant predictors of pain location, but age alone accounted for only 8% of the variance, and age and smoking together accounted for only 5% of the variance. Smoking is associated with higher levels of back pain and spinal degeneration increases with age. While there are no studies exploring smoking with location of pain in individuals with spinal degeneration, it is possible that higher estimations of pain, including more widespread estimations of pain location may be related in smokers. Using analysis of variance, BMI was not found to influence pain location. With chi-square testing, sex, depression and worker's compensation were not related to pain location (only 3 subjects had worker's compensation insurance). There were no patient characteristic variables that were sufficient to explain pain location (back pain only, back pain and leg pain, leg pain only). It is likely that these variables also had no influence over pain location.

Discussion of Associations between Patient Characteristics and Physical Function.

Since two separate measures of physical function were available in the database to measure physical function, separate statistical testing was conducted with the ODI and the physical function subscale of the SF-36. These results will be described in the following section.

First, the patient characteristics of BMI, sex, age, smoking, employment status and depression were examined with ODI scores as the dependent variable. Because the variable insurance type had several levels, this was added in a subsequent step. Initially, BMI, smoking

and employment status were significant, explaining 15.4% of the variance in ODI scores. Higher BMI and smoking were associated with worse ODI scores, while being employed was associated with better ODI scores. Next, insurance type was added, with the previously significant variables of BMI, smoking and employment status. BMI, smoking, having commercial or Medicare insurance were all significant, explaining 18% of the variance in ODI scores. Higher BMI and smoking were associated with worse ODI scores, while having commercial or Medicare insurance were associated with better ODI scores. These findings are consistent with previous findings, that higher BMI and smoking are associated with worse physical function (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn et al, 2013). Also, having insurance has been associated with better health outcomes in general, consistent with the findings in this study (Greenstein, Moskowitz, Gelijns & Egorova, 2012; Kruper, et al., 2011; McClelland, Guo & Okuyemi, 2011; Yorio, Yan, Xie & Gerber, 2012). However, the variables studied explained only 18% of the variance, leaving 82% of the variance in ODI scores unexplained. The sample size may have been too small to detect larger effects with these variables.

The combined effects of BMI, sex, age, smoking, employment status and depression were examined for their effects on SF-36 physical function subscale scores. BMI, age, employment status and depression were significant in the final model, explaining 17.7% of the variance in SF-36 physical function scores. Specifically, higher BMI, older age and depression were associated with worse SF-36 physical function subscale scores, while being employed was associated with better SF-36 physical function subscale scores. Next, insurance type was added, with the previously significant variables of BMI, older age, depression and employment status. In the final model, BMI, age, smoking and having Medicaid insurance were significant, predicting

18.2% of the variance in SF-36 physical function subscale scores. Specifically, higher BMI, older age, smoking, and having Medicaid insurance were all associated with worse SF-36 physical function subscale scores. However, the variables studied explained only 18.2% of the variance, leaving almost 82% of the variance unexplained by the study variables. It is possible that the sample size was too small to detect a larger effect.

The factors found to be associated with physical function in this study include BMI, smoking, age, and the insurance types of Medicaid, Medicare or Commercial insurance. The factors common to both ODI and SF-36 physical function subscale scores are higher BMI and smoking, having deleterious effects on both measures of physical function. The findings that BMI and smoking have a negative effect on physical function in this population are consistent with previous research (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn, et al., 2013). Medicare and Commercial insurance is positively associated with physical function in this study. It is likely that Medicare and Commercial insurance plans have better coverage for interventions such as physical therapy and spinal injections that improve physical function in this population. The finding that Medicaid insurance is associated with worse physical function is also likely due to reduced coverage for physical therapy and spinal injections.

The factors associated with ODI and SF-36 physical function subscale scores did differ. While Medicare and Commercial insurance were positively associated with ODI scores, they were not significant for SF-36 physical function subscale scores. And, while older age and Medicaid insurance were negatively associated with SF-36 physical function scores, they were not significant for ODI scores. This difference may be due to the ODI being a lumbar-specific physical function measure and the SF-36 being a generic measure of overall well-being.

To summarize, the study variables smoking, having Medicaid insurance, and not having insurance were weakly associated with pain VAS, explaining 13% of the variance. There were no patient characteristic variables that were sufficient to explain the symptoms of numbness and weakness. It is likely that these variables had no influence over the symptoms of numbness, weakness, or pain location. Finally, there were no patient characteristic variables that were sufficient to explain pain location (back pain only, back pain and leg pain, leg pain only). It is possible that these variables also had no influence over pain location.

Higher BMI, smoking, older age and having Medicaid insurance were all associated with worse physical function scores, while having commercial insurance was associated with better physical function scores. These findings are expected because they are consistent with previous literature associating higher BMI and smoking with worse physical function (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn, et al., 2013) and indigent insurance plans with worse health outcomes in general (Greenstein, Moskowitz, Gelijns & Egorova, 2012; Kruper, et al., 2011; McClelland, Guo & Okuyemi, 2011; Yorio, Yan, Xie & Gerber, 2012).

Finally, since a very small number of subjects had worker's compensation insurance, it was not possible to obtain findings that supported the literature associating worker's compensation with worse physical function outcomes for individuals with lumbar degenerative conditions.

Discussion of Additional Results

Analysis of variance was computed to determine if location of pain was associated with worse physical function. After multiple comparison testing, the presence of back and leg pain was associated with worse ODI scores. However, using analysis of variance and multiple comparison testing, the presence of back and leg pain was not significantly associated with

worse SF-36 physical function scores. These findings partially support previous findings that have associated the presence of back and leg pain with worse physical function (Kongstead, Kent, Albert, Jensen & Manniche, 2012). Since the ODI is a lumbar-specific measure of physical function, it is possible this instrument is more sensitive than the physical function subscale of the SF-36 to the relevant factors that influence physical function in this population, hence the significant association between the presence of back and leg pain together and worse physical function for the ODI, but not for the SF-36 physical function subscale.

Discussion of Results for Specific Aim 2

The purpose of Specific Aim 2 was to develop a predictive model for physical function in persons with lumbar degenerative conditions, using symptoms (back and/or leg pain, numbness, and weakness) and physiological, situational, and psychological patient factors. Since there were two measures of physical function, the ODI and the physical function subscale of the SF-36, separate statistical tests were used. First, the results of testing with ODI scores as the dependent variable will be discussed.

Using the significant predictors for ODI score from the Aim 1 analysis (smoking and BMI), symptoms were added into an analysis of variance. With general linear modeling, BMI, smoking, pain VAS and extremity numbness were significantly associated with ODI scores, explaining almost 35% of the variance. Specifically, higher BMI, smoking, higher pain VAS and the presence of extremity numbness was associated with worse ODI scores. The association between higher BMI, smoking, and higher pain level are consistent with previous research (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn et al, 2013). The finding of extremity numbness associated with worse ODI scores is unexpected, and the explanation for this is unclear. It is possible that numbness of the lower limb and foot impairs proprioception,

thereby interfering with mobility. A search of the literature revealed no studies exploring the relationship of extremity numbness and physical function in individuals with lumbar degenerative conditions. Since the ODI is a lumbar-specific measure of physical function, it is possibly more sensitive to the factors that may impact physical function in this population. Numbness of the lower extremity may be a relevant symptom for its effects on physical function in individuals with lumbar degenerative conditions.

Next, the significant predictors for SF-36 physical function scores from Aim 1 analysis (BMI, age and smoking) were added into an analysis of variance with symptoms. BMI, age and pain VAS were significant and kept in the final model. These variables were entered into a backwards step-wise multiple regression with the SF-36 physical function subscale the dependent variable. BMI, age and pain VAS were significantly associated with worse SF-36 physical function subscale scores, explaining 26% of the variance. Specifically, higher BMI, older age and higher pain level are associated with worse SF-36 physical function subscale scores. These findings are consistent with previous research associating higher BMI and higher pain level with worse physical function (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn et al, 2013). Older age has been associated with greater degenerative changes in the lumbar spine (Cheung, et al, 2009; Kalichman, Kim, Li, Guermazi & Hunter, 2010).

Higher BMI was a relevant factor in predicting worse physical function measured by both the ODI and the SF-36 physical function subscale. This finding was expected and consistent with previous literature (Prasarn, Horodyski, Behrend, Wright & Rechtine, 2012; Rihn et al, 2013). Higher BMI is associated with back pain, also a significant predictor of physical function in this study, as measured by both the ODI and the SF-36 physical function subscale. Smoking and extremity numbness were significant predictors for worse ODI scores but not worse SF-36

physical function subscale scores. Smoking is associated with higher levels of back pain, also a significant predictor of worse ODI scores in this study. Smoking also may have an effect on physical function through its effect on pulmonary function, a relationship not explored in this study. Lower extremity numbness may be a relevant factor for physical function in individuals with lumbar degenerative conditions, and detectable only by ODI scores because the ODI is a lumbar-specific physical function measure. Age was a significant predictor for worse SF-36 physical function subscale scores, but not for ODI scores. Older age is associated with more degenerative lumbar changes (Cheung, et al., 2009). In summary, the significant predictors for reduced physical function in this study are expected, and some variables are known to affect the others. The discrepancy between the significant predictors of ODI scores and SF-36 physical function scores may be related to the particular sensitivities of each instrument.

The findings of this study add to science by connecting the significant patient physiological, situational and psychological characteristics to symptoms and to physical function in a population affected by lumbar degenerative conditions. Much of the medical literature with this population does not consistently consider the impact of symptoms on physical function. By identifying the relevant physiological, situational and psychological factors that combine with symptoms to predict physical function, a risk assessment may allow early identification of individuals with characteristics that place them at risk for poorer physical function. Moreover, by studying symptoms with other well-studied patient characteristics for their combined effects on physical function, this study considers how the patient perception of symptoms affects physical function. Using patient-reported information and patient identified priorities in the plan of care with the identified risk factors may transform a standardized model of care for patients with lumbar degenerative conditions to an individualized approach to care.

This study also illustrates the need for multiple instruments to adequately measure physical function in this population. The multiplicity of patient factors significantly associated with physical function in this study also highlights the complex nature of spinal degenerative conditions and their effects on patients. Last, this study illustrates the need for development of instruments to capture the patient experience of symptoms particular to lumbar degenerative conditions, including the dimensions of distress, duration, quality and intensity. More robust data regarding the symptoms experienced by this population will enhance the understanding of the relationship of symptoms to physical function in this population.

Discussion of Study Results for Exploratory Aim 3

The purpose of Exploratory Aim 3 was to explore the impact of the physiological factor genotype (disc structural genes and pain genes) on symptoms (back and/or leg pain, numbness, and weakness) and on physical function (ODI scores and SF-36 physical function subscale scores). First, the relationship between genotype and symptoms will be examined. Next, associations between genotype and physical function will be reviewed.

Discussion of Associations between Genotype and Symptoms.

Using analysis of variance, *COL9A2, COL9A3, OPRM1, COMT* and *VDR* SNPs were analyzed for their associations with pain VAS. There were no statistically significant relationships between *COL9A2, COL9A3, OPRM1, COMT* and *VDR* SNPs and pain VAS. There was a trend toward higher pain VAS in individuals homozygous for A/A *OPRM1* genotype, lower pain VAS for individuals who were A/G, and the lowest pain VAS for individuals homozygous for G/G. Although this finding was not statistically significant, the trend is consistent with other findings associating the *G *OPRM1* allele with decreased pain sensitivity in men after lumbar disc herniation (Olsen et al, 2012). However, the literature supporting this is

inconsistent. Some studies have identified a sex specific interaction with the *G allele and pain sensitivity in individuals with lumbar disc herniation, with *G males experiencing reduced pain intensity and *G females experiencing increased pain intensity after disc herniation (Hasvik, Schistad, Grovle, Haug, Roe & Gjerstad, 2014; Olsen et al, 2012). The findings from this exploratory Aim are consistent with some previous findings in the literature, and larger sample size would allow for further exploration of the sex interaction with genotype in this population.

ACAN VNTR was tested for association with pain VAS using correlation. No statistically significant relationship was found between *ACAN* VNTR and pain VAS (r^2 = -.047, *p*. = .821).

Using chi-square, *COL9A2*, *COL9A3*, *OPRM1*, *COMT* and *VDR* were tested for associations with pain location (back pain only, back pain and leg pain, leg pain only) and numbness and weakness. There were no statistically significant associations between genotype and pain location, numbness or weakness.

When the relationship between *ACAN* VNTR and pain location (back pain only, back and leg pain, leg pain only) was analyzed with chi-square, no significant association was identified (x^2 = 17.011, *p*. = .149). It is likely that the genotype sample size was too small to identify significant associations between SNPs and symptoms, given the seven different *ACAN* VNTR alleles identified in the genotyped subjects. Also, there was limited variability in SNPs represented within the *COL9A3* and *OPRM1* genes, thus not allowing for adequate comparison of diverse SNPs with phenotype. Further study with larger sample sizes could reveal more significant findings. In particular, future questions regarding the representation of different alleles in larger populations would improve understanding of the relationship between genotype and phenotype. Future studies should illuminate which candidate genes exert the most

significant influences on symptoms and physical function in this population. Other candidate genes should be included in future studies to detect their contributions as well. Because substances involved in disc degeneration have also been identified, genes encoding for these substances should also be included in future studies, to explore their relationship to symptoms and physical function in this population.

Last, there were no associations in the literature between genotype and numbness and weakness. Thus, the findings of no significant association between genotype and numbness and weakness are not unexpected.

Discussion of Associations between Genotype and Physical Function.

Since two separate measures of physical function were used, separate statistical tests were conducted with the ODI and the physical function subscale of the SF-36. These results will be described in the following section.

Using analysis of variance, *COL9A2*, *COL9A3*, *OPRM1*, *COMT* and *VDR* SNPs were tested for association with ODI scores. There were no significant associations between *COL9A2*, *COL9A3*, *COMT* or *VDR* SNPs and ODI scores. However, there was a significant association between *OPRM1* and ODI scores. Individuals with A/A genotype were found to have significantly higher (worse) ODI scores than those with one or two copies of the G allele. And, while there were no significant associations between *COL9A2*, *COL9A3*, *OPRM1*, *COMT* or *VDR* SNPs and SF-36 physical function subscale scores with analysis of variance, when *OPRM1* was analyzed as a dichotomous variable (A/A and */G), there was a significant association between *OPRM1* and SF-36 physical function subscale scores, consistent with the findings for ODI scores. Individuals with A/A genotype (or no copies of the G allele) were found to have significantly lower (worse) SF-36 physical function subscale scores than those with one or two

copies of the G allele (*/G). These findings are consistent with previous research suggesting a difference between A/A and */G alleles and pain and physical function in individuals with herniated lumbar discs. Olsen et al., (2012) identified a sex and genotype interaction that influenced differences in individuals pain VAS and ODI scores over time after treatment for lumbar disc herniation. While the */G males had greater improvements in pain VAS and ODI scores after treatment for lumbar disc herniation than A/A males, */G females had the least improvement in pain VAS and ODI scores compared to */G males, A/A males, and A/A females. The small sample size (n = 28) limits the ability to examine sex and genotype interaction for *OPRM1*, but these findings support the connection between pain and physical function in this population.

Correlations were computed to test the relationship between *ACAN* VNTR alleles and ODI and SF-36 physical function subscale scores. There were no significant correlations between *ACAN* VNTR alleles and physical function.

In summary, the only gene found to have significant associations with physical function was *OPRM1*, and the findings were partially consistent with what has been identified in the literature. And, although not statistically significant, *OPRM1* did show a trend toward association with pain VAS. However, the literature is not consistent with regard to the genotype universally associated with greater pain experience (Olsen, et al., 2012; Walter & Lotsch, 2009).

Study Limitations

The limitations of this study include the descriptive, cross-sectional design and the use of secondary data. The cross-sectional design limits the ability to establish a temporal relationship between the predictors and the outcome. Therefore, while associations between patient physiological, situational and psychological factors and symptoms and physical function can be

determined by statistical analysis, the lack of a prospective design limits the conclusions regarding the nature of temporal relationships between patient characteristics and symptoms and physical function.

This study, though conducted using a random sample, reflects findings from one tertiary spine center located in West Michigan. The findings therefore may not be generalizable to other populations. Indeed, the study population measures of physical function were worse than expected, and worse than populations with other similar and more severe lumbar conditions, comparing study population physical function scores to scores of populations with spinal metastatic disease and disc herniations.

The presence of depression was based on review of the medical record received from the referring physician in this study and not measured directly. The validity of this variable and the interpretation of its significance in this study were therefore limited.

Information regarding medical co-morbidities and their effects on symptoms and physical function was not examined in this study. Medical co-morbidities may have accounted for some of the unexplained variance in physical function in this study. This study is therefore limited in its ability to explain all of the possible variables that may have affected physical function.

Although the organizing framework used was the TOUS, limited detail on symptoms was explored in this study. Pain VAS, location of pain, numbness and weakness were the symptoms studied. In reality, there may be more pertinent and influential symptoms that affect the outcome of physical function in these subjects. Also, this study did not distinguish between those individuals with acute lumbar spinal conditions or chronic spinal conditions. The nature of the acuity of the condition may have affected the symptom experience and/or the outcome of physical function.

While it was suggested by the author that an explanation for the association between having Medicaid and not having insurance and worse physical function may have been lack of coverage for evidence-based treatments such as physical therapy and spinal injections, this relationship was not studied.

Data on patient characteristics, symptoms and physical function predates genotyping data by as many as four years but this should not affect interpretation of results. Genotype does not change over time and the subjects in this study possessed their genotypes at the time that data were collected on patient characteristics, symptoms and physical function. The difficulty experienced in contacting potential subjects for genotyping was largely related to persons not answering phones and some phone numbers being disconnected. There was as many as five years between some subjects presentation to the spine service for care and attempts to contact those same subjects for genotyping. It is possible that those potential genotyping subjects with disconnected or changed phone numbers represented a subset of individuals with lower socioeconomic status and as such, may have affected the true randomness of the genotyping sample.

With regard to genotype, the multiple comparisons performed may lead to identification of significant results that are attributable to random chance. Therefore, the finding of a significant association of *OPRM1* genotype to physical function as measured by the ODI and SF-36 physical function subscale scores should be interpreted with caution.

Last, while the list of analgesic, non-steroidal anti-inflammatory, anti-convulsant and narcotic medications taken by subjects at the time of their initial evaluation at the spine service was recorded, medication use could not be factored into the statistical analysis. The doses were not consistently recorded in the medical record, nor were the frequency or last dose taken.

Information regarding medications taken for other medical co-morbidities were not recorded in this study and may have influenced physical function. Therefore, the influence of medication on symptoms and physical function could not be determined in this study. Medication use could have influenced subjects' estimations of their symptoms and their physical function.

Implications for Nursing Practice

The results of this study provided limited support for the usefulness of the TOUS to organize the approach to study of the phenomena related to lumbar degenerative conditions. There were significant associations between the physiological characteristic smoking and the situational characteristic of insurance type (Medicaid and no insurance) and the symptom of pain VAS. Two physiological characteristics (BMI and smoking) and one situational characteristic insurance type (commercial and Medicare insurance) were found to be associated with physical function (ODI scores). Two physiological characteristics (BMI and smoking) and one situational characteristic insurance type (medicaid) were found to be associated with physical function (SF-36 physical function subscale scores).

The patient characteristics of BMI, genotype and smoking and the symptoms of higher pain VAS and extremity numbness were useful in predicting physical function as expressed by ODI scores. The patient characteristics of BMI, genotype and age and the symptom of higher pain VAS were useful in predicting physical function as expressed by SF-36 physical function subscale scores. There were no associations identified between the psychological characteristic depression and symptoms or physical function. Thus, while there was some support for the influence of patient characteristics on symptoms and physical function in this study, the evidence was not strong.

Based on the relationships between the variables in this study, it seems imperative that nurses and health care providers include interventions targeted at the physiological characteristics of obesity and smoking in order to reduce symptoms and improve physical function. The standard care approaches that are focused on identifying the anatomic pain generator will no longer be sufficient. Incorporating interventions aimed at reducing BMI and smoking cessation with teaching regarding the effects of obesity and smoking on back pain and physical function should be an integral part of spine care. Tailored approaches that incorporate change theory and patient preferences can be developed to target the patient characteristics that are significantly associated with worse physical function outcomes.

Based on the relationships identified between pain VAS and physical function, nurses and health care professionals should focus on techniques to reduce pain. Finally, since insurance type was found to have associations with the symptom of pain VAS and physical function, healthcare professionals should advocate for consistency in coverage for all insurance plans for evidence-based interventions such as physical therapy and injections, to reduce pain and improve physical function.

Even though the propositions of the TOUS were only partially supported, organizing care for individuals with lumbar degenerative conditions based on the theory may provide more comprehensive care than the current standard care. Specifically, assessment that includes physiological, situational and psychological factors could identify risk factors that if addressed early, could reduce symptoms and maintain physical function. Current approaches that address only the presumed anatomic pain generator and do not incorporate patient characteristics that place patients at risk for worse physical function may not be sufficient to produce meaningful improvements in physical function. An awareness of the associations between patient

characteristics and symptoms and their effects on physical function could allow nurses and healthcare providers to intervene early to preserve physical function through tailored approaches that incorporate the identified risks and the preferences for that individual. The multiplicity of factors that are associated with symptoms and physical function in this population requires a trans-disciplinary approach that incorporates nurses, physicians, pain care providers, behavioral specialists and physical therapists.

Implications for Research

Because the use of the TOUS in this study was not sufficient to explain a significant portion in the variability in symptoms and physical function, other models may need to be considered for organizing the approach to study of the factors that influence the outcome of physical function in this population. One such model is the Disablement Process, described as a "socio-medical" model (Verbrugge & Jette, 1994). Disablement is conceptualized as a pathway on a continuum, moving from pathology to impairments to functional limitations to disability. This pathway is influenced by factors external to the individual, factors within the individual, and other attributes considered to be risk factors that elevate the probability of disability. These factors may speed or slow the disablement process. Acute and chronic conditions are included in the model, and the authors discuss interventions aimed at slowing the disablement process. The disablement process model may provide more salient variables and useful propositions for organizing the approach to study in this population.

There are no studies evaluating the combined effects of numbness and weakness on physical function in this population. Future studies should consider analyzing numbness and weakness together, in order to determine whether these symptoms catalyze each other in their effect on physical function. Numbness may affect physical function because of a loss of

sensation involving the foot, affecting proprioception. Weakness may affect physical function through interference with normal gait mechanics and trips. Together, these symptoms may have a greater influence on physical function than either symptom alone.

Further studies examining the frequency of back pain alone, back pain and leg pain together and leg pain alone for their effects on physical function could help health professionals identify and stratify those at risk for worse physical function. Though different anatomic pain generators in the spine share similar pain patterns (Taylor, Coxon & Watson, 2013; Cohen & Raja, 2007; van der Werff, Buijs & Groen, 2006), there is limited knowledge regarding the effects of pain patterns on physical function.

Measuring the influence of patient characteristics and genotype on symptoms and physical function over time would allow nurse scientists to determine temporal relationships between these variables. A longitudinal design could aid in determining the effects of patient characteristics on patient's response to treatment for lumbar degenerative conditions, thereby indentifying those at risk for poorer responses to treatment.

This study highlights the need for further research that includes other important patient characteristics that may influence symptoms and physical function in persons with lumbar degenerative conditions. There was unexplained variance accounting for the effects of patient characteristics on symptoms and physical function, suggesting that other as yet unidentified variables may play a role. Important variables for future study may include race, ethnicity and socioeconomic status (SES) in order to discover other relevant factors to include in a risk assessment for individuals with lumbar degenerative conditions. Associations between ethnicity and representation of SNPs would provide further insight into how genotypes are represented in

different populations and their effects on symptoms and physical function specific to those populations.

Since Aim 3 was exploratory, the genes selected for study were based on a review of those most commonly studied in relationship to the structure of the intervertebral disc and those related to the experience of pain. There are many other genes that have been studied relative to disc structure and to compounds that have been shown to affect the rate and severity of disc degeneration. None of the genes encoding for substances that affect the rate and severity of disc degeneration were included in this study.

Larger sample sizes for genotyping could provide more evidence for the connections between genotype and phenotype in this population, as well as more information regarding the representation of genotype in different ethnic populations. Caution should be used, however, when interpreting the results of these multiple comparisons because of the likelihood of finding significant results that are the result of chance alone.

Since the psychological characteristic depression was not measured directly in this study, future research should incorporate a method to measure this variable directly. This would strengthen the validity of this variable and the conclusions made regarding the associations between depression and symptoms and physical function in this population.

This study also highlights the issue of a lack of instruments to measure symptoms in individuals with lumbar degenerative conditions. While there are existing instruments to measure pain, the unique features of the symptoms that accompany lumbar degenerative conditions (the nature, location, characteristics of back and limb pain, with numbness and weakness) may require measurement techniques that are sensitive to these features. A spinal stenosis symptom measure has been developed and tested, (Stucki et al., 1996). More work must

be done to develop and refine instruments for measuring symptoms and their impact in individuals with lumbar degenerative conditions.

There were different results for the statistical tests involving physical function as measured by the ODI and the SF-36 physical function subscale. This finding reflects that the ODI is clearly a disease-specific instrument designed to measure physical function in the population of individuals with lumbar degenerative conditions, and is superior to the physical function subscale of the SF-36 for this purpose.

Finally, this study provides limited support for the use of the TOUS as an organizing framework for future studies on the effects of patient characteristics in persons with lumbar degenerative conditions. This study partially supports the notion that different categories of patient characteristics have an influence on symptoms and physical function in this population. The concept of how symptoms interact with patient characteristics and their combined effects on physical function has not been sufficiently explored. This may represent an important opportunity for nurses to add to the body of knowledge by incorporating the study of symptoms with other patient characteristics for their effects on physical function in persons with lumbar degenerative conditions. Revisions to the TOUS may improve its use in the future. Better definitions of the specific patient physiological, situational and psychological characteristics may improve the testability of the model and its use in clinical practice. As the science of genotype and phenotype progresses, it would be helpful to define how this is incorporated into the TOUS—does it fit as a physiological variable?

Implications for Policy

Obesity and smoking have been identified as an important health concerns in the U.S. This study suggests that obesity and smoking are also specific concerns in persons with lumbar

degenerative conditions for their effects on symptoms and physical function. Spine care programs should incorporate interventions designed to address all of the risk factors that affect symptoms and physical function in this population and should include specific interventions that target weight loss and smoking cessation.

This study also identified associations between insurance plans and pain and physical function in this population. Specifically, not having insurance or having Medicaid insurance was associated with higher pain scores and worse physical function. Conversely, having Medicare or Commercial insurance was associated with better physical function scores on the ODI. This difference may be due to better coverage with Medicare and Commercial insurance for evidence-based interventions such as spinal injections and physical therapy, designed to reduce pain and improve physical function in this population. Steps should be taken to provide for consistency in coverage for evidence-based interventions like spinal injections and physical therapy across insurance plans. Consideration should be given for providing coverage for weight loss treatments in this population. Because these data were collected before implementation of the Affordable Care Act, the scope and effects of coverage provided under these insurance plans is not yet known.

Last, the body of knowledge related to the use of genotyping for personalized medicine is a growing field of study. Controversy exists surrounding the implications of the use of genotyping and confidentiality issues. While the science of genotype and phenotype in populations with spinal degeneration is still developing, this information could provide helpful knowledge in the future to reduce pain and maintain physical function. This study raises questions regarding which genes contribute the most to symptoms and physical function in this population. Genes involved in the breakdown of the intervertebral disc were not included in this

study, and should be considered in combination with disc structural genes and genes associated with the experience of pain, in order to further explore the relationship of genotype to symptoms and physical function in individuals with lumbar degenerative conditions.

Conclusion/Summary

The primary purpose of this study was to examine the patient characteristics and symptoms that contribute to the outcome of physical function in a population experiencing lumbar degenerative conditions. Additionally, the novel physiological patient characteristic genotype was explored for its association with symptoms and physical function.

The physiological characteristic (smoking) and the situational characteristics (Medicaid insurance and no insurance) had significant negative influences on pain VAS. Higher BMI, smoking, older age and Medicaid insurance were significantly associated with worse physical function, while having Commercial insurance or Medicare were significantly associated with better physical function.

The variables of patient physiological, situational and psychological characteristics and symptoms were analyzed in order to develop a predictive model for the outcome physical function. Higher BMI and higher pain VAS were significant predictors for worse physical function for both the ODI and the SF-36 physical function subscale scores, while smoking and the presence of numbness were significant predictors for worse ODI scores and older age was a significant predictor of worse SF-36 physical function subscale scores. Both measures of physical function were available in the database that was used for the variables tested in this study, so both were used in the analysis and analyzed separately. The differences in the variables that predicted physical function scores between the two instruments were likely related to the

ODI being a lumbar-specific instrument and the SF-36 being a multi-purpose measure of functional health and well-being.

Last, a small sample (n = 28) of the study population provided saliva samples for genotyping. Genotype data for 4 genes implicated in maintaining disc structure and 2 genes implicated in the experience of pain were collected and analyzed for associations with symptoms and physical function. There was limited diversity of SNPs for the *COL9A3* and the *OPRM1* genotypes. While there were no statistically significant associations between genotype and symptoms, *OPRM1* genotype was significantly associated with physical function scores.

The findings from this study are an important first step that connects patient characteristics (including genotype) and symptoms to show their influence on physical function in persons with lumbar degenerative conditions. This study also raises important questions regarding which genes have the greatest impact with other patient characteristics on symptoms and physical function for individuals with lumbar degenerative conditions. Genes known to influence the breakdown of the intervertebral disc were not studied, and could be included in future studies. Other candidate genes known to influence intervertebral disc structural integrity should also be included in future studies.

APPENDICES

Appendix A: Figures

Figure 1

The Theory of Unpleasant Symptoms with Study Variables

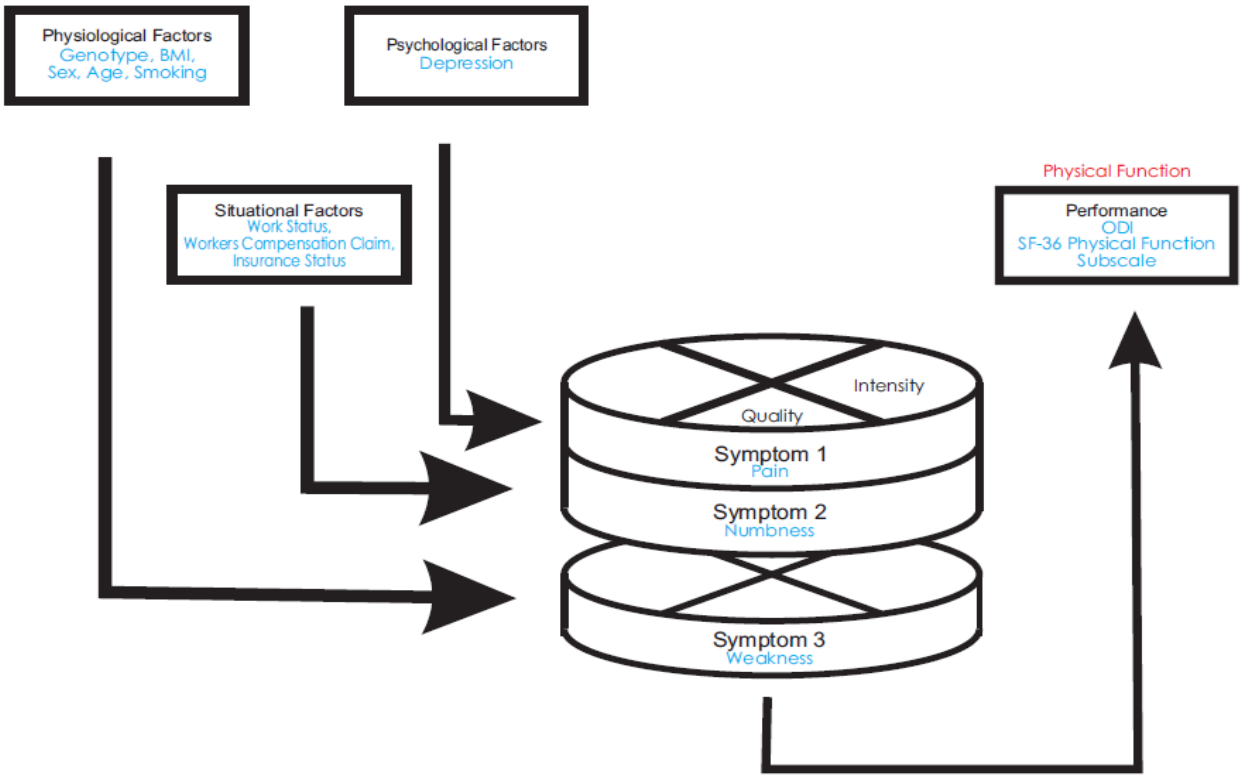


Figure 2

Neurosurgery/Spine Health History

Neurosurgery / Spine Health History

Date:_____ Patient Name: _____

Date of Birth:_____ Age: _____ Male: _____ Female: _____ ☐ Right or ☐ Left Handed

Home Address:_____ City/State/Zip: _____

Home Phone: _____ Cell Phone: _____ Work Phone _____

Emergency Contact:_____ Relation to You:_____ Phone:_____

What Physician sent you here?_____

Address:_____ Phone:_____

Who is your regular family physician?_____

Address:_____ Phone:_____

What other physicians (if any) have you seen for this problem?_____

What is your problem or complaint?_____ Work-related? ☐ Yes ☐ No

When did this episode begin?_____ Symptoms started in: neck / back or arm / leg

Describe the onset of symptoms:_____

_____

Has the pain ☐ remained the same or ☐ changed/spread? To where?_____

My back/neck pain is ☐ getting better ☐ staying the same ☐ getting worse.

What position do you sleep in? _____

My leg/arm pain is ☐ getting better ☐ staying the same ☐ getting worse. The pain is ☐ constant ☐ comes and goes.

What percent of your pain is back/neck? _____ What percent of your pain is leg/arm? _____

On a scale of 0 to 10, please rate your pain (10 is the highest intensity of pain and 0 is the lowest intensity).

0 1 2 3 4 5 6 7 8 9 10

What makes the pain worse?_____

What makes the pain better?_____

Problems with bowel or bladder function? ☐ Yes ☐ No

If yes, please describe:_____

Check the tests that have been completed & list dates. Where completed? _____

☐ X-rays _____ ☐ Blood Tests _____ ☐ EMG/NCT _____ ☐ Bone Scan _____

☐ CT Scan _____ ☐ MRI _____ ☐ Other:_____ ☐ Myelogram _____

6583-018 (logo revised 7-1-13)

Figure 2 (cont'd)

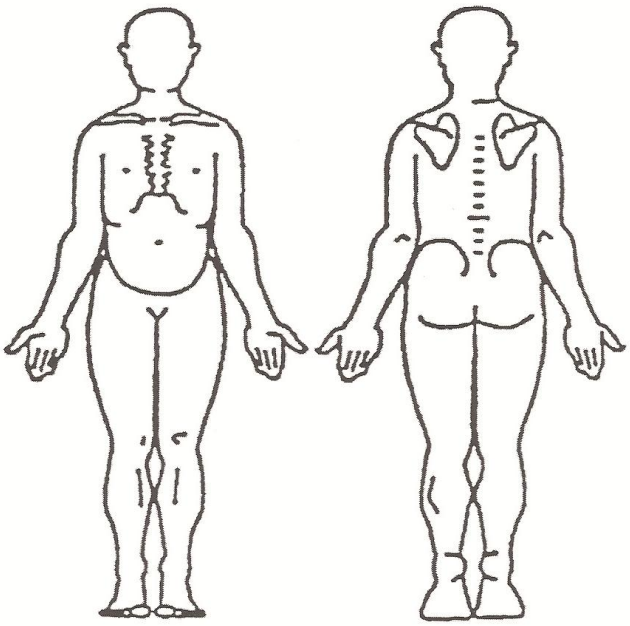
Patient Name:_____ DOB:_____ Page 2

Where is your pain now? Mark the areas on your body where you feel the described sensations. Use the appropriate symbol. Include all affected areas. To complete the picture, please draw in your face.

Ache: ^ ^ ^ ^ *Numbness:* O O O O *Pins & Needles:* = = = =

Burning: X X X X *Stabbing:* / / / /

FRONT BACK



Right Left Left Right

What previous treatments have you had and how helpful were they?

	Very	Somewhat	Not Helpful
☐ Surgery	☐	☐	☐
☐ Medications	☐	☐	☐
☐ Spinal Injections	☐	☐	☐
☐ Brace	☐	☐	☐
☐ Physical Therapy	☐	☐	☐
☐ Ice	☐	☐	☐
☐ Bedrest	☐	☐	☐
☐ Chiropractic	☐	☐	☐

Figure 2 (cont'd)

Patient Name: _____ DOB: _____ Page 3

Review of Systems (Check all that apply.)	
General	**Gastrointestinal**
_____ fever / chills	_____ trouble swallowing
_____ night sweats	_____ heartburn
_____ decreased appetite	_____ blood in stools
_____ unplanned weight loss	_____ black tarry stools
Skin	_____ diarrhea
_____ rashes	_____ constipation
_____ sores	**Urinary**
_____ eczema/psoriasis	_____ pain / burning with urination
Eyes	_____ blood in urine
_____ double / blurred vision	_____ incontinence
_____ floaters / spots	_____ kidney stones
_____ glaucoma	**Musculoskeletal**
_____ decreased field of vision	_____ joint pain / swelling / stiffness
Head / Ears / Nose / Neck / Throat	_____ arthritis / gout
_____ headaches	**Neurologic**
_____ sinus trouble	_____ blackouts
_____ hearing problems	_____ seizures
_____ hoarseness	_____ tremors
_____ swollen glands	_____ MS / ALS / MD
Respiratory	_____ memory problems
_____ wheezing	**Psychiatric**
_____ productive cough	_____ anxiety / depression
_____ shortness of breath	_____ bipolar
_____ bronchitis	_____ other psych illness
Cardiac	
_____ chest pain / tightness	
_____ irregular heartbeat	
_____ murmurs	
_____ palpitations	

Past Medical History Have you ever had or do you now have any of the following listed conditions?						
	Yes	**No**			**Yes**	**No**
Diabetes	☐	☐		Osteoporosis	☐	☐
High Blood Pressure	☐	☐		Depression / Other Psych Illness	☐	☐
Cancer (Type)	☐	☐		Stroke or TIA	☐	☐
Hepatitis	☐	☐		Epilepsy / Convulsions	☐	☐
High Cholesterol	☐	☐		Arthritis / Gout / Rheumatoid	☐	☐
Asthma	☐	☐		Thyroid Problems	☐	☐
Emphysema / COPD	☐	☐		Kidney Trouble / Dialysis / Prostate	☐	☐
Bleeding Disorder	☐	☐		Reflux / Stomach / Bowel Problems	☐	☐
Blood Clots	☐	☐		Unplanned Weight Loss	☐	☐
Heart Trouble / Chest Pain	☐	☐		Problems with Anesthesia	☐	☐
Cardiologist Name: _____				Fibromyalgia	☐	☐

Figure 2 (cont'd)

Patient Name: _____ DOB:_____ Page 4

Past Surgical History List all the surgeries you have had with the approximate dates.

1. _____ 4. _____ 7. _____
2. _____ 5. _____ 8. _____
3. _____ 6. _____ 9. _____

Family History Please list any health problems in your family members, including cause of death if deceased.

Father: _____ Mother: _____

Siblings:_____ Children: _____

Social History

Marital Status: ☐ Married ☐ Divorced ☐ Single ☐ Widowed ☐ Separated. How many times per week do you exercise? _____ Do you use tobacco? ☐ Yes ☐ No ☐ Quit date _____

What type (chew, pipe, cigarettes, etc.) How much/many per day?_____ How many years? _____

Do you use alcohol? ☐ No ☐ Yes How much per week?_____

Do you use "recreational" or IV drugs? ☐ No ☐ Yes Type/frequency:_____

Work History

Who is your current employer?_____ How long?_____

Status: ☐ Full Time ☐ Part Time ☐ Disabled ☐ Retired ☐ Homemaker. What is your current occupation/type of work? _____ Currently working? ☐ No ☐ Yes Hours per week? _____

If not currently working, when was last date worked?_____

Is any litigation or insurance settlement regarding pain/accident/injury pending? ☐ No ☐ Yes

If yes, please explain:_____

_____

(Caseworker name, if applicable: _____)

Physician Signature: _____ Date Reviewed: _____

Addendum

Date:_____

6583-018 (logo revised 7-1-13) neuroadmn/rm/Neuroscience Program/Health-History.doc original date 1-15-09

Figure 3

SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c Lifting or carrying groceries	☐1	☐2	☐3
d Climbing several flights of stairs	☐1	☐2	☐3
e Climbing one flight of stairs	☐1	☐2	☐3
f Bending, kneeling, or stooping	☐1	☐2	☐3
g Walking more than a mile	☐1	☐2	☐3
h Walking several hundred yards	☐1	☐2	☐3
i Walking one hundred yards	☐1	☐2	☐3
j Bathing or dressing yourself	☐1	☐2	☐3

Figure 3 (cont'd)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

Figure 3 (cont'd)

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

Figure 3 (cont'd)

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Figure 4

IRB Approval

NOTICE OF EXPEDITED NEW IRB APPROVAL Page 1 of 2

MERCY HEALTH

200 Jefferson Ave. SE – Grand Rapids, MI 49503
P: 616.685.6198

To: Teri Holwerda, PhD-c, RN, ONC, ACNS-BC
Mercy Health
200 Jefferson, SE
Grand Rapids, MI 49503

Re: IRB# 13-0816-01-SM
The Effects of Individual Characteristics and Symptoms on Physical Function in Persons with Lumbar Degenerative Conditions

Date: September 5, 2013

This is to inform you that Mercy Health Saint Mary's Institutional Review Board (IRB) has approved the above research study by expedited review. This includes approval for:

- Protocol DRAFT 7, no version date
- Research Informed Consent Form, no version date
- SF-36v2 Health Survey, US Version 2.0
- Oswestry Low Back Pain Scale

The approval period is from **September 5, 2013** to **September 4, 2014. Your study number is 13-0816-01-SM.** Please be sure to reference this number and/or your study title in any correspondence with the IRB.

Your responsibilities to the IRB do not end with this approval. You will be required to submit a continuing review report by the date indicated below or a notification of study closure form with a report of the study's findings upon completion of the study.

Continued approval is conditional upon your compliance with the following requirements:

- A copy of the **Informed Consent Form**, approved as of **September 5, 2013**, is enclosed. No other consent form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject must be given a copy of the signed consent form.

- 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.

NOTICE OF EXPEDITED NEW IRB APPROVAL Page 2 of 2

- Significant changes to the study site and significant deviations from the research protocol and all unanticipated problems that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research must be promptly reported to the IRB.
- All forms of advertising (including but not limited to: television, radio, internet, flyers, brochures, posters) must be submitted to the IRB and must not be implemented until approved by the IRB
- Unanticipated problems/events and adverse events, *whether related to the study article or not,* must be reported to the IRB. Contact the IRB office for the appropriate form.
- Please complete and submit reports to the IRB as follows:

  Renewal of the study - complete and return the Continuing Review Report/Request for Renewal by **08/01/2014.** The study cannot continue after **September 4, 2014** until re-approved by the IRB.

  Closure of the study – complete and return the Notification of Study Closure form.

Please call me if you have any questions about the terms of this approval.

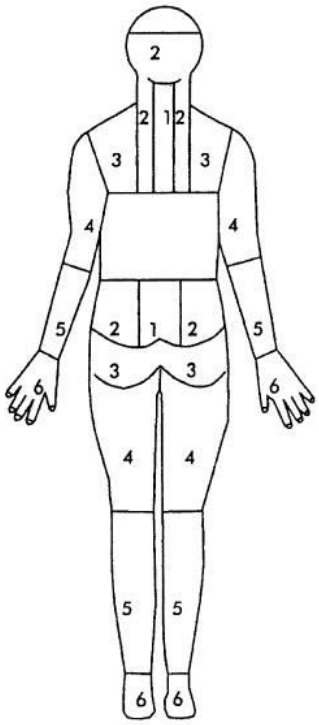
Brenda Hoffman

Brenda Hoffman
IRB Chairperson

Copy: File

Figure 5

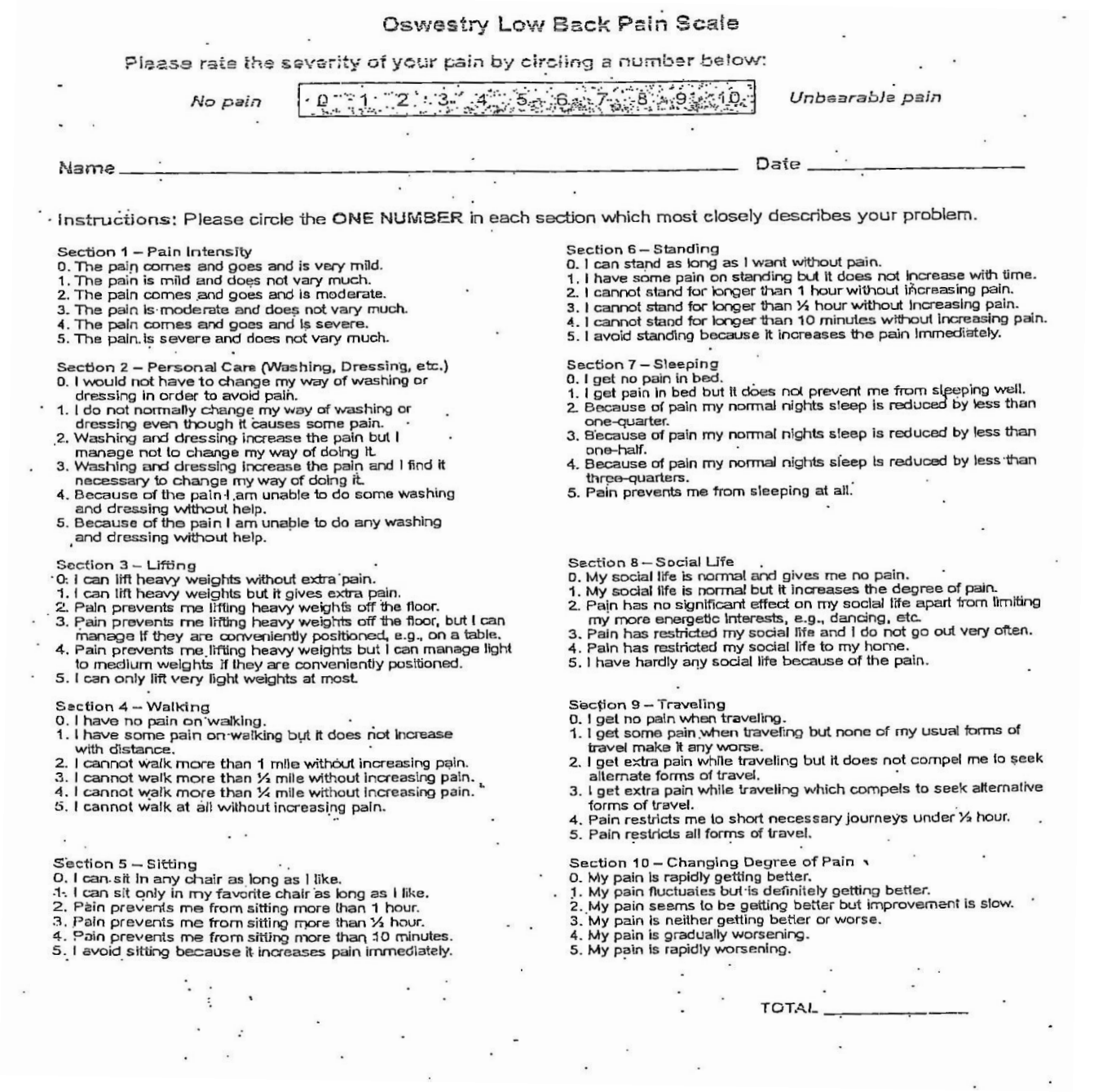
Pain Diagram Overlay



Management of Non-radicular Low Back Pain: A Pilot Clinical Trial. *Manual Therapy, 11*, 279-286.

Appendix B

Oswestry Disability Index



Oswestry Low Back Pain Scale

Please rate the severity of your pain by circling a number below:

No pain 0 1 2 3 4 5 6 7 8 9 10 *Unbearable pain*

Name _____ Date _____

Instructions: Please circle the **ONE NUMBER** in each section which most closely describes your problem.

Section 1 – Pain Intensity
0. The pain comes and goes and is very mild.
1. The pain is mild and does not vary much.
2. The pain comes and goes and is moderate.
3. The pain is moderate and does not vary much.
4. The pain comes and goes and is severe.
5. The pain is severe and does not vary much.

Section 2 – Personal Care (Washing, Dressing, etc.)
0. I would not have to change my way of washing or dressing in order to avoid pain.
1. I do not normally change my way of washing or dressing even though it causes some pain.
2. Washing and dressing increase the pain but I manage not to change my way of doing it.
3. Washing and dressing increase the pain and I find it necessary to change my way of doing it.
4. Because of the pain I am unable to do some washing and dressing without help.
5. Because of the pain I am unable to do any washing and dressing without help.

Section 3 – Lifting
0. I can lift heavy weights without extra pain.
1. I can lift heavy weights but it gives extra pain.
2. Pain prevents me lifting heavy weights off the floor.
3. Pain prevents me lifting heavy weights off the floor, but I can manage if they are conveniently positioned, e.g., on a table.
4. Pain prevents me lifting heavy weights but I can manage light to medium weights if they are conveniently positioned.
5. I can only lift very light weights at most.

Section 4 – Walking
0. I have no pain on walking.
1. I have some pain on walking but it does not increase with distance.
2. I cannot walk more than 1 mile without increasing pain.
3. I cannot walk more than ½ mile without increasing pain.
4. I cannot walk more than ¼ mile without increasing pain.
5. I cannot walk at all without increasing pain.

Section 5 – Sitting
0. I can sit in any chair as long as I like.
1. I can sit only in my favorite chair as long as I like.
2. Pain prevents me from sitting more than 1 hour.
3. Pain prevents me from sitting more than ½ hour.
4. Pain prevents me from sitting more than 10 minutes.
5. I avoid sitting because it increases pain immediately.

Section 6 – Standing
0. I can stand as long as I want without pain.
1. I have some pain on standing but it does not increase with time.
2. I cannot stand for longer than 1 hour without increasing pain.
3. I cannot stand for longer than ½ hour without increasing pain.
4. I cannot stand for longer than 10 minutes without increasing pain.
5. I avoid standing because it increases the pain immediately.

Section 7 – Sleeping
0. I get no pain in bed.
1. I get pain in bed but it does not prevent me from sleeping well.
2. Because of pain my normal nights sleep is reduced by less than one-quarter.
3. Because of pain my normal nights sleep is reduced by less than one-half.
4. Because of pain my normal nights sleep is reduced by less than three-quarters.
5. Pain prevents me from sleeping at all.

Section 8 – Social Life
0. My social life is normal and gives me no pain.
1. My social life is normal but it increases the degree of pain.
2. Pain has no significant effect on my social life apart from limiting my more energetic interests, e.g., dancing, etc.
3. Pain has restricted my social life and I do not go out very often.
4. Pain has restricted my social life to my home.
5. I have hardly any social life because of the pain.

Section 9 – Traveling
0. I get no pain when traveling.
1. I get some pain when traveling but none of my usual forms of travel make it any worse.
2. I get extra pain while traveling but it does not compel me to seek alternate forms of travel.
3. I get extra pain while traveling which compels to seek alternative forms of travel.
4. Pain restricts me to short necessary journeys under ½ hour.
5. Pain restricts all forms of travel.

Section 10 – Changing Degree of Pain
0. My pain is rapidly getting better.
1. My pain fluctuates but is definitely getting better.
2. My pain seems to be getting better but improvement is slow.
3. My pain is neither getting better or worse.
4. My pain is gradually worsening.
5. My pain is rapidly worsening.

TOTAL _____

Appendix C

Data Collection Tool

INDIVIDUAL CHARACTERISTICS, SYMPTOMS AND PHYSICAL FUNCTION IN LUMBAR DEGENERATION

DATA COLLECTION TOOL

ID Number_____

Physiological Factors

Height_____

Weight_____

BMI calculation_____

BMI Category_____

Sex Female_____Male_____

Age_____

Smoking Y_____N_____

Genotype

OPRM-1 SNP_____

COMT SNP_____

COL9A2 SNP_____

COL9A3 SNP_____

ACAN VNTR_____

VDR SNP_____

Situational Factors

Employment Status

Currently working? Y_____N_____

Worker's Compensation claim? Y_____N_____

Insurance Type:

Commercial_____

Medicare_____

Champus_____

Medicaid_____

None_____

Psychological Factors

Depression Y_____N_____

Symptoms

Pain VAS score_____ (Measured in Cm)

Pain location

1_____

2_____

3_____

4_____

5_____

6_____

Limb Numbness Y_____N_____

Weakness Y____N____

Outcome Measures:

SF-36 Physical Function subscale score_____

ODI score_____

Medical Co-morbidities

HTN Y_____N_____

Diabetes Y_____N_____

CHD Y _____N_____

Fibromyalgia Y_____N_____

Other (list)_____

Total_____

Medications: (Record all oral medications the individual is currently taking, both scheduled and prn, in the following categories: non-steroidal anti-inflammatories(NSAIDS), steroids, analgesics and narcotics. Code 1 for NSAIDS, 2 for steroids, 3 for analgesics and 4 for narcotics.)

Medication Name:_____ Code:_____

Medication Name:_____ Code:_____

Medication Name:_____ Code:_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Medication Name:_____ **Code:**_____

Appendix D

Permission to Use TOUS

WOLTERS KLUWER HEALTH LICENSE

TERMS AND CONDITIONS

Nov 18, 2013

This is a License Agreement between Teri L Holwerda ("You") and Wolters Kluwer Health ("Wolters Kluwer Health") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Wolters Kluwer Health, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

License Number	3272201448457
License date	Nov 18, 2013
Licensed content publisher	Wolters Kluwer Health
Licensed content publication	Advances in Nursing Science
Licensed content title	The Middle-Range Theory of Unpleasant Symptoms: An Update
Licensed content author	Elizabeth R. Lenz, Linda C. Pugh, Renee A. Milligan, et al
Licensed content date	Jan 1, 1997
Volume Number	19
Issue Number	3
Type of Use	Dissertation/Thesis
Requestor type	Individual
Author of this Wolters Kluwer article	No
Title of your thesis / dissertation	The Effects of Individual Characteristics and Symptoms on Physical Function in Persons with Lumbar Degenerative Conditions
Expected completion date	Feb 2014
Estimated size(pages)	130
Billing Type	Invoice

Billing address	650 Griswold St SE
	GRAND RAPIDS, MI 49507
	United States
Total	0.00 USD
Terms and Conditions	

Terms and Conditions

1. A credit line will be prominently placed and include: for books - the author(s), title of book, editor, copyright holder, year of publication; For journals - the author(s), title of article, title of journal, volume number, issue number and inclusive pages.
2. The requestor warrants that the material shall not be used in any manner which may be considered derogatory to the title, content, or authors of the material, or to Wolters Kluwer.
3. Permission is granted for a one time use only within 12 months from the date of this invoice. Rights herein do not apply to future reproductions, editions, revisions, or other derivative works. Once the 12-month term has expired, permission to renew must be submitted in writing.
4. Permission granted is non-exclusive, and is valid throughout the world in the English language and the languages specified in your original request.
5. Wolters Kluwer cannot supply the requestor with the original artwork or a "clean copy."
6. The requestor agrees to secure written permission from the author (for book material only).
7. Permission is valid if the borrowed material is original to a Wolters Kluwer imprint (Lippincott-Raven Publishers, Williams & Wilkins, Lea & Febiger, Harwal, Igaku-Shoin, Rapid Science, Little Brown & Company, Harper & Row Medical, American Journal of Nursing Co, and Urban & Schwarzenberg - English Language).
8. If you opt not to use the material requested above, please notify Rightslink within 90 days of the original invoice date.
9. Please note that articles in the ahead-of-print stage of publication can be cited and the content may be re-used by including the date of access and the unique DOI number. Any final changes in manuscripts will be made at the time of print publication and will be reflected in the final electronic version of the issue.?Disclaimer: Articles appearing in the Published Ahead-of-Print section have been peer-reviewed and accepted for publication in the relevant journal and posted online before print publication. Articles appearing as publish ahead-of-print may contain statements, opinions, and information that have errors in facts, figures, or interpretation. Accordingly, Lippincott Williams & Wilkins, the editors and authors and their respective employees are not responsible or liable for the use of any such inaccurate or misleading data, opinion or information contained in the articles in this section.

10. 1This permission does not apply to images that are credited to publications other than Wolters Kluwer journals. For images credited to non-Wolters Kluwer journal publications, you will need to obtain permission from the journal referenced in the figure or table legend or credit line before making any use of the image(s) or table(s).
11. In case of **Disease Colon Rectum, Plastic Reconstructive Surgery, The Green Journal, Critical Care Medicine, Pediatric Critical Care Medicine, the American Heart Publications, the American Academy of Neurology** the following guideline applies: no drug brand/trade name or logo can be included in the same page as the material re-used
12. When requesting a permission to translate a full text article, Wolters Kluwer/Lippincott Williams & Wilkins requests to receive the pdf of the translated document
13. "Adaptations of single figures do not require Wolters Kluwer **further** approval if the permission has been granted previously. However, the adaptation should be credited as follows:?Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: [JOURNAL NAME] (reference citation), copyright (year of publication)"

    Please note that modification of text within figures or full-text articles is strictly forbidden.

14. The following statement needs to be added when reprinting the material in Open Access journals only: 'promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information".
15. Other Terms and Conditions:

v1.8

If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501162191.
Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.

Make Payment To:
Copyright Clearance Center
Dept 001
P.O. Box 843006
Boston, MA 02284-3006

For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.

Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.

Appendix E

Informed Consent

Research Informed Consent Form

Study Title: The Effects of Individual Characteristics and Symptoms on Physical Function in Persons with Lumbar Degenerative Conditions

Principal Investigator: Teri L. Holwerda PhD-c RN, NP

APPROVED BY MERCY HEALTH IRB
EFFECTIVE 09-05-13 TO 09-04-14

"You" refers to the subject.

"We" refers to Michigan State University College of Nursing, Mercy Health Saint Mary's and Teri L. Holwerda

1. **Introduction**
   You are being asked to participate in a clinical research study. Clinical research is the study of human diseases in an attempt to improve diagnosis and treatment. In order to decide whether or not you should agree to be part of this research study, you should receive enough information about its risks and benefits to make a judgment. This process is called informed consent. This consent form gives detailed information about the research study, which will be discussed with you. If you wish to participate in this study you will be asked to sign this form.

2. **Purpose of This Research Study**
   The purpose of this research study is to learn more about the factors that contribute to the experience of low back pain and limitation of function in persons with lumbar spinal degenerative conditions. This study is undertaken by the primary investigator as partial fulfillment of a Doctoral degree in nursing from Michigan State University College of Nursing.

   We hope to learn more about the physiological, situational and psychological factors and symptoms that cause limitation of function in persons with lumbar spinal degenerative conditions. These factors include Body Mass Index, (BMI), smoking, age, gender, whether an individual is working, worker's compensation, type of insurance, depression, and certain genes that contribute to degeneration of the disc, and genes involved in the experience of pain. We also want to better understand the symptoms experienced by individuals with lumbar spinal degenerative conditions, in order to develop interventions that improve pain and function in this population.

   The major portion of this study involves retrospective chart review of randomly selected patients who have sought care from the Saint Mary's Spine service in the past. BMI, smoking, age, gender, whether an individual is working, worker's compensation, type of insurance and depression will be analyzed to better understand the effect these factors have on reported pain and function. A small subset of patients from this group will be randomly identified to request a saliva sample in order to obtain more information regarding the genes that contribute to degeneration of the disc and genes involved in the experience of pain.

Pt. Initials_____

Saliva is a good source of genetic material. It can be collected by spitting in a small cup. The saliva samples will be tested in a laboratory at Michigan State University. Only three genes for disc structure and two genes for pain will be tested. No other genes will be analyzed. If you decide to participate in the study, you will be asked to travel to the Mercy Health Saint Mary's Spine Service in order to provide a saliva sample.

After this study is completed, the saliva samples will continue to be stored in the lab at Michigan State University, and may be used in the future to answer similar questions about the genes involved in spine degeneration and pain. The samples will be stored with coded identification numbers. You will be contacted to provide your permission before the saliva samples can be re-tested.

6. What Will Happen When You Complete the Study

When the study ends, you will not be informed of the genetic testing results, because the usefulness of genetic testing for disc degeneration and pain is still experimental. The genetic analyses performed during this study are not a form of treatment, diagnosis, or prediction of lumbar spinal degeneration.

7. Possible Risks or Side Effects of Taking Part in this Study

The risks of participating in this study are anticipated to be minimal. The procedure of collecting saliva samples causes little to no discomfort and has a minimal possibility of infection.

Participation in this study may cause anxiety related to increased awareness of how genes contribute to lumbar degenerative conditions. If this causes you anxiety, the primary investigator is able to provide you with information and reassurance that lumbar degeneration is due to many different factors, and the contribution of genes is one small part.

Insurance companies will not have access to the genetic information, so the genetic testing should not affect your ability to get and maintain insurance.

There may be unforeseeable risks for participating in this study. If we learn of new risks that we think might affect your desire to stay in the research, we will tell you.

Every effort will be made to protect your confidentiality during this study. However, there may be a risk of loss of confidentiality. The confidentiality of information about you, including BMI, gender, age, smoking status, employment status, worker's compensation claim, insurance type, depression and genetic information related to disc structure and pain may be lost.

In accordance with Michigan Public Health Code MCL 333.5133, an HIV and hepatitis test may be performed without written consent if a healthcare worker is exposed to your blood or other

Pt. Initials_____

Pt. Initials_____

bodily fluids. If the test results indicate you are HIV or hepatitis positive, you will be informed of these results and given appropriate counseling.

8. Costs for Taking Part in this Study

The only cost to you for taking part in this study involves the cost of transportation to Mercy Health Saint Mary's Spine Service to meet with the primary investigator and to provide a saliva sample. Since the study does not involve insurance, there will be no cost to your insurance company.

If you are injured as a result of your participation in this research project, Mercy Health Saint Mary's will assist you in obtaining emergency care, if necessary, for your research related injuries. If you have insurance for medical care, your insurance carrier will be billed in the ordinary manner. As with any medical insurance, any costs that are not covered or are in excess of what are paid by your insurance, including deductibles, will be your responsibility. Mercy Health Saint Mary's policy is not to provide financial compensation for lost wages, disability, pain or discomfort, unless required by law to do so. This does not mean that you are giving up any legal rights you may have. You may contact Teri L. Holwerda at 616-685-6020 with any questions or to report an injury.

9. Payment for Taking Part in this Study

You will receive a small payment for participating in this study. Payment will be in the form of a $10.00 store card to a local retailer.

10. Possible Benefits to You for Taking Part in the Study

You will not directly benefit from your participation in the study. However, your participation in this study may contribute to the understanding of the physiological, situational and psychological factors that affect how symptoms are experienced for patients with lumbar degenerative conditions. This information may help health care professionals ease the symptoms experienced by these patients.

11. About Participating in this Study

The Primary Investigator for this study may have been the Mercy Health Saint Mary's Spine Service provider who cared for you at the time of your visit(s) to the Spine Service. You are not under any obligation to participate in any research project offered by your care provider. Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the investigator.

Your doctor or the investigator may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions. If

Pt. Initials_____

privacy. You personal information may be disclosed if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

15. Financial Conflict of Interest

The primary investigator has no financial conflicts related to this study. The primary investigator will not benefit in any financial way from this study. This study will help the primary investigator to complete a doctoral degree in nursing from Michigan State University College of Nursing.

16. HIPAA Authorization

As part of this research study, you are being asked to release your health information. The Health Insurance Portability and Accountability Act (HIPAA) permits a hospital or doctor's office to use or release protected health information (PHI) for the purposes of treatment, payment or health care operations. A HIPAA authorization gives permission from you to use or release PHI for research purposes, and is in addition to your consent to participate in this research study. The investigator, Teri L. Holwerda, will use and share personal health information about you. *This is information about your health that may also include your name, address, telephone number or other facts that could identify the health information as yours.* This includes information in your medical record and information created or collected during the study. This information may include your medical history, physical exam and laboratory test results. Some of these tests may have been done as part of your regular care. The investigator will use this information about you to complete this research.

In most cases, the investigator will use your initials and assign a code number to your information. Regulatory authorities and the Mercy Health Saint Mary's Institutional Review Board may also review or copy your information to make sure that the study is done properly or for other purposes required by law.

By signing this Authorization, you allow the investigator to use your personal health information to carry out and evaluate this study. You also allow the investigator to share your personal health information with:

- The Mercy Health Saint Mary's Institutional Review Board
- Other regulatory agencies—e.g. National Institutes of Health (NIH) and Department of Health and Human Services (DHHS)

Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, these groups are committed to keeping your personal health confidential.

You have the right to see and get a copy of your records related to the study for as long as the investigator has this information. However, by signing this Authorization you agree that you

Pt. Initials_____

might not be able to review or receive some of your records related to the study until after the study has been completed.

You may choose to withdraw this Authorization at any time, but you must notify the investigator. Send your written withdrawal notice to Teri L. Holwerda, PhD-c RN NP Mercy Health Saint Mary's Spine Service, Hauenstein Center, 245 Cherry St. SE, Grand Rapids, MI 49503. Or call Teri L. Holwerda at 616-685-6020. If you withdraw from the study and withdraw your Authorization, no new information will be collected for study purposes. This Authorization does not have an expiration date.

If you do not sign this authorization, you cannot participate in the genetic testing. Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

17. Names of Contacts for Questions About the Study

If you have any questions about taking part in this study, or in the event of a research related illness or injury, contact Teri L. Holwerda, 616-685-6020. If you have any questions about your rights as a research participant, you may contact:

Brenda Hoffman, Mercy Health Saint Mary's Institutional Review Board (IRB) Chairperson
200 Jefferson Ave. SE Grand Rapids, MI 49503
Telephone: 616-685-6198

Pt. Initials_____

DOCUMENTATION OF INFORMED CONSENT

By signing this consent form and HIPAA authorization and by initialing each page, you certify you have read this form, you have had the opportunity to ask question about this study and this form, and you have received answers that fully satisfy those questions. You are voluntarily signing this consent form and HIPAA authorization as evidence of your decision to participate in this research study and you are giving authorization for release of all your protected health information relative to this research.

You are aware you may withdraw your consent and HIPAA authorization in writing or by phone at any time without harming your future medical care or losing any benefits to which you might be otherwise entitled. You have been advised that the investigator in charge of this study may discontinue your participation in this study if it is felt to be in your best interest, if you do not follow the study requirements or if the study is stopped.

You will receive a signed copy of this Research Informed Consent Form and HIPAA Authorization.

By signing this consent form, you have not waived any of your legal rights or released the parties involved in this study from liability for negligence.

Signature of Study Participant	Date
Printed Name of Study Participant	Date
Signature of Person Obtaining Consent	Date
Signature of Principal Investigator	Date

Pt. Initials_____

Appendix F

Data Use Agreement

DATA USE AGREEMENT

This Data Use Agreement ("Agreement") is entered into by and between Trinity Health-Michigan d/b/a Mercy Health Saint Mary's and all of its affiliated and controlled healthcare organizations, ("Saint Mary's") and Michigan State University ("Recipient" or "Limited Data Set Recipient"), for its researcher Dr. Barbara Given ("Recipient Investigator") and Recipient Investigator's PH.D. candidate Teri Holwerda, PhD-c, RN, ONC, ACNS-BC ("PhD Candidate") and applies to all services and relationships between Saint Mary's and Recipient.

A. HIPAA Dominance. In the event of a conflict or inconsistency between the terms of any other agreement between the parties, regarding the Limited Data Set being provided under this agreement, and this language, this language controls. This language is required by the Health Insurance Portability and Accountability Act of 1996, as amended, and all final regulations issued pursuant to such Act ("HIPAA").

B. Preparation of the Limited Data Set. Saint Mary's may engage the Recipient to prepare the Limited Data Set, as further described in Exhibit A, in accordance with the HIPAA Regulations. Furthermore, once the Recipient has completed the preparation of the Limited Data Set, the Recipient shall return or destroy the information that includes the direct identifiers.

C. Limited Data Set - Use and Disclosure. Limited Data Set Recipient may only use or disclose the Limited Data Set information received or created by it, (a) to perform its obligations under this Agreement consistent only with research, public health or limited health care operations purposes, including without limitation, the following: The clinical research study entitled "The Effects of Individual Characteristics and Symptoms on Physical Function in Persons with Lumbar Degenerative Conditions, Saint Mary's IRB# 13-0816-01-SM ("Research Study"), in order to properly manage and administer its business, (b) to carry out its legal responsibilities if the disclosure is required by law, or (c) for permitted data aggregation functions, as defined by HIPAA. Recipient may not use or disclose Limited Data Set information in a manner that would violate HIPAA if the Recipient were a covered entity thereunder.

D. Recipient's Disclosure – Class of Persons Permitted to Use or Receive the Limited Data Set. If the Recipient discloses the Limited Data Set information to others, the Recipient must obtain reasonable assurances from the person to whom the information is disclosed that it will be held confidentially and used or further disclosed only as required by law or for the purpose for which it is disclosed to the person and the person notifies Recipient of any instances of which it is aware that the confidentiality of the information has been breached. The Recipient may only disclose Limited Data Set information to and permit the following persons or classes of persons to use such information: Michigan State University College of Nursing Dissertation Committee members and/or faculty, or other persons as may be agreed upon between Saint Mary's and Recipient in writing from time to time.

E. Recipient Not to Re-Identify or Contact Individuals. Recipient will not identify or attempt to identify the individual(s) to which the Limited Data Set information pertains or contact or attempt to contact the individual(s) that Recipient believes to be the subject of any Limited Data Set information.

F. Safeguards. Recipient agrees to implement reasonable administrative, physical and technical safeguards to protect the confidentiality, integrity and availability of the Limited Data Set along with any other PHI. Recipient agrees to implement reasonable electronic security practices for Saint Mary's Limited Data Set along with any other PHI which is transmitted, stored, received, or used in electronic form.

G. Reports. Recipient will (i) promptly report to Saint Mary's any use or disclosure of the Limited Data Set or any PHI not permitted by this HIPAA language; (ii) any successful security incident of which Recipient becomes aware; and (iii) in summary form, upon request of Saint Mary's, any unsuccessful security incident of which Recipient becomes aware. If the definition of "Security Incident" in the HIPAA regulation is modified to remove the requirement for reporting "unsuccessful" security incidents, section (iii) above shall no longer apply as of the effective date of such regulation modification.

H. Subcontractors. Recipient shall ensure its permitted subcontractor(s) (if subcontractors are permitted) are advised in writing of Recipient's obligations with respect to the Limited Data Set along with any other PHI. Recipient shall require that the permitted subcontractor(s) agree in writing to the same restrictions and obligations as the Recipient. Permitted subcontractors of the Recipient must agree to implement reasonable administrative, physical and technical safeguards to protect the confidentiality, integrity and availability of the Limited Data Set along with any other PHI.

Authorized representatives of the parties have executed this as of the last date written below.

SAINT MARY'S

Name: Bill Ma

Title: PRESIDENT

Date: 5/8/14

MICHIGAN STATE UNIVERSITY

Name:

Title:

Richard W. Chytla
Executive Director
MSU Technologies

Date: 5.05.14

Investigator's Acknowledgement:
Investigator acknowledges that she/he has read, understands, and fully accepts the obligations under this Agreement.

Barbara Given

Dr. Barbara Given, University Distinguished Professor
Date: 4/30/14

REFERENCES

REFERENCES

Abraham, J., Maranian, M., Spiteri, I., Russell, R., Ingle, S., Luccarini, C., Earl, H., Pharoah, P., Dunning, A. & Caldas, C. (2012). Saliva samples are a viable alternative to blood samples as a source of DNA for high throughput genotyping. *BMC Medical Genomics, 5*, retrieved from http://www.biomedcentral.com/1755-8794/5/1/19

Ahles, T., Ruckdeschel, J. & Blanchard, E. (1984). Cancer-related pain—II. Assessment with visual analogue scales. *Journal of Psychosomatic Research, 28*, 121-124.

Aladin, D., Cheung, K., Chan, D., Jim, J., Luk, K. & Lu, W. (2007). Expression of the *Trp2* allele of *COL9A2* is associated with alterations in the mechanical properties of human intervertebral discs. *Spine, 32*, 2820-2826.

Altinkaya, N., Yildirim, T., Demir, S., Alkan, O. & Sarica, F. (2011). Factors associated with thickening of the ligamentum flavum is thickening of the ligamentum flavum thickening due to hypertrophy or buckling? *Spine, 36*, E1093-E1097.

Anderson, P., Schwaegler, P., Cizek, D. & Leverson, G. (2006). Work status as a predictor of surgical outcome of discogenic low back pain. *Spine, 31*, 2510-2515.

Anderson, P., Subach, B. & Riew, D. (2009). Predictors of outcome after anterior cervical discectomy and fusion a multivariate analysis. *Spine, 34*, 161-166.

Annunen, S., Paassilta, P., Lohiniva, J., Perala, M., Pihlajamaa, T., Karppinen., J., Tervonen, O., Kroger, H., Lahde, S., Vanharanta, H., Ryhanen, L., Goring, H., Ott, J., Prockop, D. & Ala-Kokko, L. (1999). An allele of *COL9A2* associated with intervertebral disc disease. *Science, 285*, 409-412.

Argoff, C. (2010). Clinical implications for opioid pharmacogenetics. *Clinical Journal of Pain, 26*, S16-20.

Armstrong, T. (2003). Symptoms experience: A concept analysis. *Oncology Nursing Forum, 30*, 601-606.

Atlas, S., Chang, Y., Kammann, E., Keller, R., Deyo, R. & Singer, D. Long-term disability and return to work among patients who have a herniated lumbar disc: The effect of disability compensation. *Journal of Bone & Joint Surgery, 82A*, 4-15.

Atlas, S., Deyo, R., Patrick, D., Convery, K., Keller, R. & Singer, D. (1996). The Quebec Task Force classification for spinal disorders and the severity, treatment, and outcomes of sciatica and lumbar spinal stenosis. *Spine, 21*, 2885-2892.

Balmain, N., Hauchecorne, M., Pike, J., Cuisinier-Gleizes, P. & Mathieu, H. (1993). Distribution and subcellular immunolocalization of 1,25-dihydroxyvitamin D3 receptors in rat epiphyseal cartilage. *Cellular and Molecular Biology (Noisy-le-grand). 39,* 339-50.

Battie, M., Videman, T., Gill, K., Moneta, G., Nyman, R., Kaprio, J. & Koskenvuo, M. (1991). 1991 Volvo Award in clinical sciences. Smoking and lumbar intervertebral disc degeneration: An MRI study of identical twins. *Spine, 16,* 1015-1021.

Battie, M., Videman, T., Levalahti, E., Gill, K. & Kaprio, J. (2007). Heritability of low back pain and the role of disc degeneration. *Pain, 131,* 272-280.

Battie, M. Videman, T., Levalahti, E., Gill, K. & Kaprio, J. (2008). Genetic and environmental effects on disc degeneration by phenotype and spinal level a multivariate twin study. *Spine, 33,* 2801-2808.

Beaton, D. & Schemitsch, E. (2003). Measures of health-related quality of life and physical function. *Clinical Orthopaedics and Related Research, 413,* 9-105.

Behrend, C., Prasarn, M., Coyne, E., Horodyski, M., Wright, J. & Rechtine, G. (2012). Smoking cessation related to improved patient-reported pain scores following spinal care. *Journal of Bone & Joint Surgery, 94,* 2161-2166.

Bener, A., Verjee, M., Dafeeah, E., Falah, O., Al-Juhaishi, T., Schlog, J., Sedeeq, A. & Khan, S. (2013). Psychological factors: Anxiety, depression and somatization in low back pain patients. *Journal of Pain Research, 6,* 95-101.

Benoist, M., Boulo, P. & Hayem, G. (2012). Epidural steroid injections in the management of low-back pain with radiculopathy: An update on their efficacy and safety. *European Spine Journal, 21,* 204-213.

Bogduk, N. (2012). Degenerative joint disease of the spine. *Radiologic Clinics of North America, 50,* 613-628.

Brant, J., Beck, S. & Miaskowski, C. (2010). Building dynamic models and theories to advance the science of symptom management research. *Journal of Advanced Nursing, 66,* 228-240.

Burnham, R., Warren, S., Saboe, L., Davis, L., Russell, G. & Reid, D. (1996). Factors predicting employment 1 year after traumatic spine fracture. *Spine, 21,* 1066-1071.

Busija, L., Osborne, R., Nilsdotter, A., Buchbinder, R. & Roos, (2008). Magnitude and meaningfulness of change in SF-36 scores in four types of orthopedic surgery. *Health and Quality of Life Outcomes, 6,* 1-12. doi: 10.1186/1477-7525-6-55

Cai, C., Pua, Y. & Lim, K. (2007). Correlates of self-reported disability in patients with low back pain: The role of fear-avoidance beliefs. *Annals of the Academy of Medicine, Singapore, 36*, 1013-1020.

Carragee, E., Alamin, T., Miller, J. & Carragee, J. (2005). Discographic, MRI and psychosocial determinants of low back pain disability and remission: A prospective study in subjects with benign persistent back pain. *The Spine Journal, 5*, 24-35.

Cawthon, P., Fox, K., Gandra, S., Delmonico, M., Chiun-Fang, C., Anthony, M., Caserotti, P., Kritschevsky, S., Newman, A., Goodpaster, B., Satterfield, S., Cummings, S. & Harris, T. (2011). Clustering of strength, physical function, muscle and adiposity characteristics and risk of disability in older adults. *Journal of the American Geriatric Society, 59*, 781-787.

Centers for Disease Control and Prevention, 2014. *Prevalence of Self-Reported Obesity Among U.S. Adults*. Retrieved from: http://www.cdc.gov/obesity/data/adult.html

Centers for Disease Control and Prevention, 2014. *Adult Cigarette Smoking in the United States: Current Estimates*. Retrieved from: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/

Chapman, J., Norvell, D., Hermsmeyer, J., Bransford, R., De Vine, J., Mc Girt, M. & Lee, M. (2011). Evaluating common outcomes for measuring treatment success for chronic low back pain. *Spine, 36*, S54-S68.

Cheng, J., Lee, M., Massicotte, E., Ashman, B., Gruenberg, M., Pilcher, L. & Skelly, A. (2011). Clinical guidelines and payer policies on fusion for the treatment of chronic low back pain. *Spine, 36*, S144-S163.

Cheung, K., Karppinen, J., Chan, D., Song, Y., Sham, P., Cheah, K., Leong, J. & Luk, K. (2009). The prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine, 34*, 934-940.

Cheung, K., Samartzis, D., Karppinen, J. & Luk, K. (2012). Are "patterns" of lumbar disc degeneration associated with low back pain? New insights based on skipped level disc pathology? *Spine, 37*, E430-E438.

Chokshi, F., Quencer, R. & Smoker, W. (2010). The "thickened" ligamentum flavum: Is it buckling or enlargement? *American Journal of Neuroradiology, 31*, 1813-1816.

Choma, T., Schuster, J., Norvell, D., Dettori, J. & Chutkan, N. (2011). Fusion versus non-operative treatment for chronic low back pain do comorbid diseased or general health factors affect outcome? *Spine, 36*, S87-S95.

Chou, W., Yang, L., Lu, H., Ko, J., Wang, C., Lin, S., Lee, T., Concejero, A. & Hsu, C. (2006). Association of μ-opioid receptor gene polymorphism (A118G) with variations in

morphine consumption for analgesia after total knee arthorplasty. *Acta Anaesthesiologica Scandinavica, 50*, 787-792.

Chung-Wei, C., McAuley, J., Macedo, L., Barnett, D., Smeets, R., & Verbunt, J. (2011). Relationship between physical activity and disability in low back pain: A systematic review and meta-analysis. *Pain, 152*, 607-613.

Cleland, J., Childs, J., Palmer, J. & Eberhart, S. (2006). Slump stretching in the management of non-radicular pain: A pilot clinical trial. *Manual Therapy, 11*, 279-286.

Cleland, J., Gillani, R., Bienen, J. & Sadosky, A. (2010). Assessing dimensionality and responsiveness of outcomes measures for patients with low back pain. *Pain Practice, 11*, 57-69.

Cohen, S. & Raja, S. (2007). Pathogenesis, diagnosis and treatment of lumbar zygapophysial (facet) joint pain. *Anesthesiology, 106*, 591-614.

Cork, R., Isaac, I., Elsharydah, A., Saleemi, S., Zavisca, F. & Alexander, L. (2004). A comparison of the Verbal Rating Scale and the Visual Analog Scale for pain assessment. *Internet Journal of Anesthesiology, 8*, 1-4.

Corwin, E., Brownstead, J., Barton, N., Heckard, S & Morin, K. (2005). The impact of fatigue on the development of postpartum depression. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 34*, 577-586.

Corwin, E., Klein, L. & Rickelman, K. (2002). Predictors of fatigue in healthy young adults: Moderating effects of cigarette smoking and cancer. *Biological Research for Nursing, 2*, 222-233.

Crook, J., Milner, R., Schultz, I. & Stringer, B. (2002). Determinants of an occupational disability following a low back injury: A critical review of the literature. *Journal of Occupational Rehabilitation, 12*, 277-295.

Dai, F., Belfer, I., Schwartz, C., Banco, R., Martha, J., Tigioughart, H., Tromanhouser, S., Jenis, L. & Kim, D. (2010). Association of *catechol-O-methyltransferase* genetic variants with outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. *The Spine Journal, 10*, 949-957.

Daffner, S., Hymanson, H., & Wang, J. (2010). Cost and use of conservative management of lumbar disc herniation before surgical discectomy. *Spine, 10*, 463-468.

Dagenais, S., Caro, J. & Haldeman, S. (2008). A systematic review of low back pain cost of illness studies in the United States and internationally. *The Spine Journal, 8*, 8-20.

Dasenbrock, H., Wolinsky, J., Sciubba, D., Witham, T., Gokaslan, Z. & Bydon, A. (2012). The impact of insurance status on outcomes after surgery for spinal metastases. *Cancer, 118*, 4833-4841.

Davidson, M. & Keating, J. (2002). A comparison of five low back disability questionnaires: Reliability and responsiveness. *Physical Therapy, 82*, 8-24.

Downie, W., Leatham, P., Rhind, V., Wright, V., Branco, J. & Anderson, J. (1978). Studies with pain rating scales. *Annals of the Rheumatic Diseases, 37*, 378-381.

Deyo, R., Mirza, S., Martin, B., Kreuter, W., Goodman, D. & Jarvik, J. (2010). Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *Journal of the American Medical Association, 303*, 1259-1265.

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E., Humphreys, J., Lee, K., Miaskowski, C., Puntillo, K., Rankin, S., & Taylor, D. (2001). Advancing the science of symptom management. *Journal of Advanced Nursing, 33*, 668-676.

Edward, R., Smith, M., Klick, B., Magyar-Russell, G., Haythornthwaite, J., Holavanahalli, R., Patterson, D., Blakeney, P., Lezotte, D., McKibben, J., & Fauerbach, J. (2007). Symptoms of depression and anxiety as unique predictors of pain-related outcomes following burn injury. *Annals of Behavioral Medicine, 34*, 313-322.

Eggermont, L., Milberg, W., Lipsitz, L., Scherder, E. & Leveille, S. (2009). Physical activity and executive function in aging: The MOBILIZE Boston study. *Journal of the American Geriatric Society, 57*, 1750-1756.

El-sayed, A., Ziewacz, J., Davis, M., Lau, D., Siddiqi, H., Zamora-Berridi, G. & Sullivan, S. (2012). Insurance status and inequalities in outcomes after neurosurgery. *World Neurosurgery, 76*, 459-466.

Eser, B., Cora, T., Eser, O., Kalkan, E., Haktanir, A., Erdogan, M. & Solak, M. (2010). Association of the polymorphisms of vitamin D receptor and aggrecan genes with degenerative disc disease. *Genetic Testing and Molecular Biomarkers, 14*, 313-317.

Fairbank, J., Couper, J., Davies, J. & O'Brien, J. (1980). The Oswestry low back pain questionnaire. *Physiotherapy, 66*, 271-273.

Fairbank, J., Gwilym, S., France, J., Daffner, S., Dettori, J., Hermsmeyer, J. & Andersson, G., (2011). The role of classification of chronic low back pain. *Spine, 36*, S19-S42.

Fairbank, J., & Pynsent, P. (2007). The Oswestry disability index. *Spine, 25*, 2940-2953.

Falco, F., Manchikanti, L., Datta, S., Sehgal, N., Geffert, S., Onyewu, O., Zhu, J., Coubarous, S., Hameed, M., Ward, S., Sharma, M., Hameed, H., Singh, V & Boswell, M. (2012). An update of the effectiveness of therapeutic lumbar facet joint interventions. *Pain Physician, 15*, E909-E953.

Farrar, J., Berlin, J., & Strom, B. (2003). Clinically important changes in acute pain outcome measures: A validation study. *Journal of Pain and Symptom Management, 25*, 406-411.

Farrell, D. & Savage, E. (2010). Symptom burden in inflammatory bowel disease: Rethinking conceptual and theoretical underpinnings. *International Journal of Nursing Practice, 16*, 437-442.

Fawcett, F. (2005). Framework for analysis and evaluation of nursing theories. In Fawcett, J. (2005). *Contemporary nursing knowledge analysis and evaluation of nursing models and theories* (2nd Ed.). (pp. 441-449). Philadelphia: F.A. Davis Company.

Ferrans, C., Johnson Zerwic, J., Wilbur, J., & Larson, J. (1999). Conceptual model of health-related quality of life. *Journal of Nursing Scholarship, 37*, 336-342.

Ferreira, M. & Pereira, M. (2013). The mediator role of psychological morbidity in patients with chronic low back pain in differentiated treatments. Journal of Health Psychology, doi: 10.1177/1359105313488970

Fillingim, R., Kaplan, L., Staud, R., Ness, T., Glover, Tl, Campbell, C., Mogil, J. & Wallace, M. (2005). The A118G single nucleotide polymorphism of the μ-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. The Journal of Pain, 6, 159-167.

Freemont, A. (2009). The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain. *Rheumatology, 48*, 5-10.

Fritz, J. & Irrgang, J. (2001). A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. *Physical Therapy, 81*, 776-788.

Fu, M., Lemone, P. & McDaniel, R. (2004). An integrated approach to an analysis of symptom management in patients with cancer. *Oncology Nursing Forum, 31*, 65-70.

Fu, M., McDaniel, R., & Rhodes, V. (2007). Measuring symptom occurrence and symptom distress: Development of the symptom experience index. *Journal of Advanced Nursing, 59*, 623-634.

Genevay, S. & Atlas, S. (2010). Lumbar spinal stenosis. *Best Practice & Research Clinical Rheumatology, 24,* 253-265.

George, S., Coronado, R., Beneciuk, J., Valencia, C., Werneke, M. & Hart, D. (2011). Depressive symptoms, anatomical region, and clinical outcomes for patients seeking outpatient physical therapy for musculoskeletal pain. *Physical Therapy, 91*, 358-372.

Gift, A. (2009). Unpleasant Symptoms. In Peterson, S. & Bredow, T. *Middle Range Theories Application to Nursing Research* (2nd ed.) (pp. 82-98). Philadelphia: Wolters-Kluwer Health/Lippincott Williams & Wilkins.

Gift, A., Jablonski, A., Stommel, M. & Given, W. (2004). Symptom clusters in elderly patients with lung cancer. *Oncology Nursing Forum, 31*, 203-210.

Gillum, R. & Obesisan, T. (2010). Physical activity, cognitive function, and mortality in a U.S. cohort. *Annals of Epidemiology, 20*, 251-257.

Glassman, S., Copay, A., Berven, S., Polly, D., Subach, B. & Carreon, L. (2008). Defining substantial clinical benefit following lumbar spine arthrodesis. *The Journal of Bone & Joint Surgery, 90*, 1839-1847. doi: 10.2106/JBJS.G.01095

Golatowski, C., Salazar, M., Dhople, V., Hammer, E., Kocher, T., Jehmlich, N. & Volker. U. (2013). Comparative evaluation of saliva collection methods for proteome analysis. *Clinica Chimica Acta, 419*, 42-46.

Gong, X., Wang, J., Liu, F., Yuan, H., Zhang, W., Guo, Y. & Jiang, B. (2013). Gene polymorphisms of *OPRM1* A118G and *ABCB1* C3435T may influence opioid requirements in Chinese patients with cancer pain. *Asian Pacific Journal of Cancer Prevention, 14*, 2937-2943.

Greenstein, A., Moskowitz, A., Gelijns, A. & Egorova, N. (2012). Payer status and treatment paradigm for acute cholecystitis. *Archives of Surgery, 147*, 453-458.

Grotle, M., Brox, J. & Vollestad, N. (2004). Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. *Spine, 29,* E492-E501.

Gun, R., Osti. O., O'Riordan, A., Mpelasoka, F., Eckerwall, C. & Smyth, J. (2005). Risk factors for prolonged disability after whiplash injury: A prospective study. *Spine, 30*, 386-391.

Guyer, R., Siddiqui, S., Zigler, J., Ohnmeiss, D., Blumenthal, S., Sachs, B., Hochschuler, S. & Rashbaum, R. (2008). Lumbar spinal arthroplasty analysis of one center's twenty best and twenty worst clinical outcomes. *Spine, 33*, 2566-2569.

Hadjipavlou, A., Tzermiadianos, M., Bogduk, N. & Zindrick, M. (2008). The pathophysiology of disc degeneration. *The Journal of Bone and Joint Surgery, 90-B*, 1261-1270.

Hammer, J., Howell, S., Bytzer, P., Horowitz, M., & Talley, N. (2003). Symptom clustering in subjects with and without diabetes mellitus: A population-based study of 15,000 Australian adults. *The American Journal of Gastroenterology, 98*, 391-398.

Hangai, M., Kaneoka, K., Kuno, S., Hinotsu, S., Sakane, M., Mamizuka, N., Sakai, S. & Ochiai N. (2008). Factors associated with lumbar intervertebral disc degeneration in the elderly. *The Spine Journal, 8*, 732-740.

Harris, I., Mulford, J., Solomon, M., van Gelder, J. & Young, J. (2005). Association between compensation status and outcome after surgery: A meta-analysis. *Journal of the American Medical Association, 293*, 1644-1652.

Hartvigsen, J., Nielsen, J., Ohm Kyvik, K., Fejer, R., Vach, W., Iachine, I. & Leboef-Yde, C. (2009). Heritability of spinal pain and consequences of spinal pain: A comprehensive genetic epidemiologic analysis using a population-based sample of 15,328 twins ages 20-71 years. *Arthritis & Rheumatism, 61*, 1343-1351.

Hastie, B., Riley, J., Kaplan, L., Herrera, D., Campbell, C., Virtusio, K., Mogil, J., Wallace, M. & Fillingim, R. (2012). Ethnicity interacts with the *OPRM1* gene in experimental pain sensitivity. *Pain, 153*, 1610-1619.

Hasvik, E., Schistad, E., Grovle, L., Haugen, A., Roe, C. & Gjerstad, J. (2014). Subjective health complaints in patients with lumbar radicular pain and disc hernation are associated with a sex-*OPRM1 A11G* polymorphism interaction: A prospective 1-year observational study. *BMC Musculoskeletal Disorders, 15*, http://www.biomedcentral.com/1471-2474/15/161

Healthy People 2020 (2012). *Arthritis, Osteoporosis, and Chronic Back Conditons*. Retrieved from: http://healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=3

Heidrich, S., Egan, J., Hengudomsub, P., & Randolph, S. (2006). Symptoms, symptom beliefs, and quality of life of older breast cancer survivors: A comparative study. *Oncology Nursing Forum, 33*, 315-322.

Heuch, I., Hagen, K., Heuch, I., Nygaard, O. & Zwart, J. (2010). The impact of body mass index on the prevalence of low back pain: The HUNT study. *Spine, 35*, 764-768.

Heuch, I. Heuch, I., Hagen, K. & Zwart, J. (2013). Body mass index as a risk factor for developing chronic low back pain a follow up in the Nord-Trondelag Health Study. *Spine, 38*, 133-139.

Higashino, K., Matsui, Y., Yagi, S., Takata, Y., Goto, T., Sakai, T., Katoh, S. & Yasui, N. (2007). The alpha2 type IX collagen tryptophan polymorphism is associated with the severity of disc degeneration in younger patients with herniated nucleus pulposus of the lumbar spine. *International Orthopaedics (SICOT), 31*, 107-111.

Hirano, K., Imagama, S., Hasegawa, Y., Ito, Z., Muramotot, A. & Ishiguro, N. (2014). Impact of low back pain, knee pain, and timed up-and-go test on quality of life in community-living people. *Journal of Orthopaedic Science, 19*, 164-171.

Hobart, J., Williams, L., Moran, K. & Thompson, A. (2002). Quality of life measurement after stroke: Uses and abuses of the SF-36. *Stroke Journal of the American Heart Association, 33*, 1348-1356. doi: 10.1161/01.STR.0000015030.59594.B3

Hoffman, A.J., von Eye, A., Gift, A.G., Given, B.A., Given, C.W., & Rothert, M. (2009). Testing a theoretical model of perceived self-efficacy for cancer-related fatigue self-management and optimal physical functional status. *Nursing Research, 58*(1), 32-41.

Holliday, K. & McBeth, J. (2011). Recent advances in the understanding of genetic susceptibility to chronic pain and somatic symptoms. *Current Rheumatology Reports, 13*, 521-527. doi: 10.1007/s11926-0110208-4

Huang, C., Liu, H., Su, N., Hsu, Y., Yang, C., Chen, C & Tsai, P. (2008). Association between human opioid receptor genes polymorphisms and pressure pain sensitivity in females. *Journal of the Association of Anaesthetists of Great Britain and Ireland, 63*, 1288-1295.

Hutchinson, S. & Wilson, H. (1998). The Theory of Unpleasant Symptoms and Alzheimer's Disease. *Scholarly Inquiry for Nursing Practice, 12*, 143-158.

Jarvik, J., Hollingworth, W., Heagerty, P., Haynor, D., Boyko, D., & Deyo, R. (2005). Three-year incidence of low back pain in an initially asymptomatic cohort clinical and imaging risk factors. *Spine, 30*, 1541-1548.

Jensen, M., Karoly, P. & Braver, S. (1986). The measurement of clinical pain intensity: A comparison of six methods. *Pain, 27*, 117-126.

Jensen, M., Smith, D., Ehde, D. & Robinsin, L. (2001). Pain site and the effects of amputation pain: Further clarification of the meaning of mild, moderate, and severe pain. *Pain, 91*, 317-322.

Jhawar, B., Fuchs, C., Colditz, G. & Stampfer, M. (2006). Cardiovascular risk factors for physician-diagnosed lumbar disc herniation. *The Spine Journal, 6*, 684-691.

Jim, J., Noponen-Hietala, N., Cheung, K., Ott, J., Karppinen, J., Sahraravand, A., Luk, K., Yip, S., Sham, P., Song, Y., Leong, J., Cheah, K., Ala-Kokko, L. & Chan, D. (2005). The TRP2 allele of COL9A2 in an age-dependent risk factor for the development and severity of intervertebral disc degeneration. *Spine, 30*, 2735-2742.

Jurgens, C., Moser, D., Armola, R., Carlson, B., Sethares, K. & Riegel, B. (2009). Symptom clusters of heart failure. *Research in Nursing & Health, 32*, 551-560.

Kales, S., Linos, A., Chatzis, C., Sai, Y., Halla, M., Nasioulas, G. & Christiani, D. (2004). The role of collagen IX tryptophan polymorphisms in symptomatic intervertebral disc disease in southern European patients. *Spine, 29*, 1266-1270.

Kalichman, L. & Hunter, D. (2007). Lumbar facet joint osteoarthritis: A review. *Seminars in Arthritis and Rheumatism, 37*, 69-80.

Kalichman, L. & Hunter, D. (2008). The genetics of intervertebral disc degeneration. Associated genes. *Joint Bone Spine 75*, 388-396.

Kalichman, L., Kim, D., Li, L., Guermazi, A. & Hunter, D. (2010). Computed tomography-evaluated features of spinal degeneration: Prevalence, intercorrelation, and association with self-reported low back pain. *The Spine Journal, 10*, 200-208.

Kaptan, H., Yelcin, H. & Kasimcan, O. (2012). Correlation of low back pain caused by lumbar spinal stenosis and depression in women: A clinical study. *Archives of Orthopaedic and Trauma Surgery, 132*, 963-967.

Karahan, A, Kav, S. Abbasoglu, A. & Dogan, N. (2009). Low back pain: Prevalence and risk factors among hospital staff. *Journal of Advanced Nursing, 65*, 516-524.

Kathy, K., Harris, K., Hadi, S. & Chow, E. (2007). What should be the optimal cut points for mild, moderate, and severe pain? *Journal of Palliative Medicine, 10*, 1338-1346.

Kauppila, L. (2009). Atherosclerosis and disc degeneration/Low back pain: A systematic review. *European Journal of Vascular and Endovascular Surgery, 37*, 661-670.

Kawaguchi, Y., Kanamori, M., Ishihara, H., Ohmori, K., Matsui, H. & Kimura, T. (2002). The association of lumbar disc disease with vitamin-D receptor gene polymorphism. *The Journal of Bone and Joint Surgery, 84-A*, 2022-2028.

Kim, H. & Schwartz, C. (2010). The genetics of pain: Implications for evaluation and treatment of spinal disease. *The Spine Journal, 10*, 827-840.

Kim, H., Suh, B., Lee, D., Park, J., Kang, K., Chang, B., Lee, C. & Yeom, J. (2013). Gender difference of symptom severity in lumbar spinal stenosis: Role of pain sensitivity. *Pain Physician, 16*, E715-E723.

Kleiber, C., Schutte, C., McCarthy, A., Floria-Santos, M., Mirray, J. & Hanrahan, K. (2007). Predictors of topical analgesic effectiveness in children. *Journal of Pain, 8*, 168-174.

Kohlboeck, G., Greimel, K., Piotrowski, P., Leibetseder, M., Krombholz-Reindl, M., Neuhofer, R., Schmid, A. & Klinger, R. (2004). Prognosis of multifactorial outcome in lumbar discectomy: A prospective longitudinal study investigating patients with disc prolapse. *Clinical Journal of Pain, 20*, 455-461.

Kongsted, A., Kent, P., Albert, H., Jensen, T. & Manniche, C. (2012). Patients with low back pain differ from those who also have leg pain or signs of nerve root involvement—a cross-sectional study. *BMC Musculoskeletal Disorders, 13*. Retrieved from http://www.biomedcentral.com/1471-2474/13/236

Konstantinou, K., Hider, S., Jordan, J., Lewis, M., Dunn, K. & Hay, E. (2013). The impact of low back-related leg pain on outcomes as compared with low back pain alone: A systematic review of the literature. Clinical Journal of Pain, doi: 10.1097/AJP.obo13e31826f9a52

Kosinski, M., Keller, S., Hatoum, H., Kong, S., & Ware, J. (1999). The SF-36 health survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis. *Medical Care, 37,* MS10-MS22.

Kruper, L., Holt, A., Xu, S., Duan, L., Henderson, K., Bernstein, L. & Ellenhorn, J. (2011). Disparities in reconstruction rates after mastectomy: Patterns of care and factors associated with the use of breast reconstruction in southern California. *Annals of Surgical Oncology, 18,* 2158-2165.

LaCaille, R., DeBerard, S., LaCaille, L., Masters, K. & Colledge, A. (2007). Obesity and litigation predict workers' compensation costs associated with interbody cage lumbar fusion. *The Spine Journal, 7* 266-272.

Lachman, H., Morrow, B., Shprintzen, R., Veit, S., Parsia, S., Faedda, G., Goldberg, R., Kucherlapati, R. & Papolos, D. (1996). Association of codon 108/158 *catechol-O-methyltransferase* gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. *American Journal of Medical Genetics, 67,* 468-472.

Lee, E. (2005). Relationships of mood disturbance, symptom experience and attentional function in women with breast cancer based upon the Theory of Unpleasant Symptoms. *Journal of Korean Academy of Nursing, 35,* 728-736.

Lee, M., Dettori, J., Standaert, C., Brodt, E. & Chapman, J. (2012). The natural history of degeneration of the lumbar and cervical spines. *Spine, 37,* S18-S30.

Leidy, N. (1994). Functional status and the forward progress of merry-go-rounds: Toward a coherent analytical framework. *Nursing Research, 43,* 196-202

Lenz, E.R., Pugh, L.C., Milligan, R.A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science, 19(*3), 14-27.

Lenz, E.R., Suppe, F., Gift, A.G., Pugh, L.C., & Milligan, R.A., (1995). Collaborative development of middle-range nursing theories: Toward a theory of unpleasant symptoms. *Advances in Nursing Science, 17*(3), 1-13.

Lin, M., Hwang, H., Chen, C. & Chiu, W. (2007). Comparisons of the Brief Form of the World Health Organization Quality of Life and Short Form-36 for persons with spinal cord injuries. *American Journal of Physical Medicine and Rehabilitation, 86,* 104-113. Doi10.1097/01.phm.0000247780.64373.Oe

Lin, S., Lin, R., & Huang, L. (2006). Disability in patients with degenerative lumbar spinal stenosis. *Archives of Physical Medicine and Rehabilitation, 87,* 1250-1256.

Liu, H. (2006). Fatigue and associated factors in hemodialysis patients in Taiwan. *Research in Nursing & Health, 29,* 40-50.

Liuke, M., Solovieva, S., Lamminen, A., Luoma, K., Leino-Arjas, P., Luukkonen, R. & Riihimaki, H. (2005). Disc degeneration of the lumbar spine in relation to overweight. *International Journal of Obesity, 29*, 903-908.

Livshits, G., Popham, M., Malkin, I., Sambrook, P., MacGregor, A., Spector, T. & Williams, F. (2011). Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: The UK Twin Spine Study. *Annals of Rheumatic Diseases, 70*, 1740-1745.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I. & Taskinen, J. (1995). Kinetics of human soluble and membrane-bound *catechol-O-methyltransferase*: A revised mechanism and description of thermolabile variant of the enzyme. *Biochemistry, 34*, 4202-4210.

MacGregor, A., Andrew, T., Sambrook, P. & Spector, T. (2004). Structural, psychological, and genetic influences on low back and neck pain: A study of adult female twins. *Arthritis & Rheumatism, 51*, 160-167.

Maughan, E. & Lewis, J. (2010). Outcome measures in chronic low back pain. *European Spine Journal, 19*, 1484-1494.

McCann, K. & Boore, J. (2000). Fatigue in persons with renal failure who require maintenance haemodialysis. *Journal of Advanced Nursing, 32*, 1132-1142.

McClelland, S., Guo, H. & Okuyemi, K. (2011). Population-based analysis of morbidity and mortality following surgery for intractable temporal lobe epilepsy in the United States. *Archives of Neurology, 68*, 725-729.

McGuire, D. (1997). Measuring Pain. In M. Frank-Stromborg & S Olsen, (Eds.), *Instruments for clinical health-care research (2nd ed.)* (pp. 528-554). Sudbury, Massachusetts: Jones and Bartlett Publishers.

McHorney, C. (1996). Measuring and monitoring general health status in elderly persons: Practical and methodological issues in using the SF-36 health survey. *The Gerontologist, 36*, 571-583.

Menon, S., Lea, R., Roy, B., Hanna, M., Wee, S., Haupt, M. & Griffiths, L. (2012). The human μ-opioid receptor gene polymorphism (A118G) is associated with head pain severity in a clinical cohort of female migraine with aura patients. *The Journal of Headache and Pain, 13*, 513-519.

Miaskowski, C. (2009). Understanding the genetic determinants of pain and pain management. *Seminars in Oncology Nursing, 25*, S1-S7.

Mohamed, R., Campbell, J., Cooper-White, J., Dimeski, G. & Punyadeera, C. (2012). *Clinical and Translational Medicine, 1*, retrieved from http://www.clintransmed.com/conent/1/1/19

Mok, L. & Lee, I (2008). Anxiety, depression and pain intensity in patients with low back pain who are admitted to acute admitted to acute care hospitals. *Journal of Clinical Nursing, 17*, 1471-1480.

Monticone, M., Baiardi, P., Ferrari, S., Foti, C., Mugnai, R., Pillastrini, P., Vanti, C. & Zanoli, G. (2009). Development of the Italian version of the Oswestry Disabiltiy Index (ODI) A cross-cultural adaptation, reliability, and validity study. *Spine, 34*, 2090-2095.

Moon, H., Kim, J., Lee, H., Chotai, S., Kang, J., Suh, J. & Park, Y. (2012). Annulus fibrosus cells interact with neuron-like cells to modulate production of growth factors and cytokines in symptomatic disc degeneration. *Spine, 37*, 2-9.

Motl, R. & McAuley, E. (2009). Symptom cluster as a predictor of physical activity in Multiple Sclerosis: Preliminary evidence. *Journal of Pain and Symptom Management, 38*, 270-279.

Mura, E., Govoni, S., Racchi, M., Carossa, V., Ranzani, G., Allegri, M. & van Schaik, R. (2013). Consequences of the 118A>G polymorphism in the *OPRM*1 gene: Translation from bench to bedside? *Journal of Pain Research, 6*, 331-353.

Myers, J. (2009). Comparison of the Theory of Unpleasant Symptoms and the Conceptual Model of Chemotherapy-related Changes in Cognitive Function. *Oncology Nursing Forum, 36*, E1-E10.

Nakki, A., Videman, T., Kujala, U., Suhonen, M., Mannikko, M., Peltonen, L., Battie, M., Kaprio, J. & Saarela, J. (2011). Candidate gene association study of magnetic resonance imaging-based hip osteoarthritis (OA): Evidence for *COL9A2* gene as a common predisposing factor for hip OA and lumbar disc degeneration. *Journal of Rheumatology, 38*, 747-752.

National Center for Health Statistics, (2009). *Health, United States, 2009*. Retrieved from: http://www.cdc.gov/nchs/data/hus/hus09.pdf#053

National Institutes for Health (2014). *Health risks of obesity*. Retrieved from: http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000348.htm

National Institute for Occupational Safety and Health, (2004). *Worker Health Chartbook*. Retrieved from: http://www.cdc.gov/niosh/docs/2004-146/detail/imagedetail.asp@imgid38.htm

Nguyen, T., Randolph, D., Talmage, J., Succop, P. & Travis, R. (2011). Long-term outcomes of lumbar fusion among Workers' Compensation subjects. *Spine, 36*, 320-331.

Ohnhaus, E. & Adler, R. (1975). Methodological problems in the measurement of pain: A comparison between the verbal rating scale and the visual analogue scale. *Pain, 1*, 379-384.

Ostelo, R., Deyo, R., Stratford, P., Waddell, G., Croft, P., Von Korff, M., Bouter, L. & de Vet, H. (2008). Interpreting change scores for pain and functional status in low back pain. Toward international consensus regarding minimal important change. *Spine, 33*, 90-94.

Parks, P., Lenz, E., Milligan, R. & Han, H. (1999). What happens when fatigue lingers for 18 months after delivery? *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 28*, 87-93.

Patrick, D., Deyo, R., Atlas, S., Singer, D., Chapin, A. & Keller, R. (1995). Assisting health-related quality of life in patients with sciatica. *Spine, 20*, 1899-1908.

Pereira, L., Obara, K., Dias, J., Menacho, M., Guariglia, D., Schiavoni, D., Pereira, H. & Cardoso, J. (2012). Comparing the Pilates method with no exercise or lumbar stabilization for pain and functionality in patients with chronic low back pain: A systematic review and analysis. *Clinical Rehabilitation, 26*, 10-20.

Peterson, S. & Bredow, T. (2009). Introduction to the nature of nursing knowledge. In Peterson, S. & Bredow, T. *Middle range theories application to nursing research* (2nd Ed.). (p. 31). Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins.

Pincus, T., Burton, A., Vogel, S., Field, A. (2002). A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine, 27*, E109-E20.

Prasarn, M., Horodyski, M., Behrend, C., Wright, J. & Rechtine, G. (2012). Negative effects of smoking, worker's compensation and litigation on pain/disability scores for spine patients. *Surgical Neurology International, 3*, S388-S369. doi: 10.4103/2152-7806.103870

Prins, M., van der Wurff, M. & Groen, G. (2013). Chronic low back pain patients with accompanying leg pain: The relationship between pain extent and pain intensity, disability and health status. *Journal of Back and Musculoskeletal Rehabilitation, 26*, 55-61.

Pugh, L., Milligan, R. & Lenz, E. (2000). Response to "Insomnia, fatigue, anxiety, depression and quality of life of cancer patients undergoing chemotherapy". *Scholarly Inquiry for Nursing Practice, 14*, 291-294.

Rajaee, S., Bae, H., Kanim, L. & Delamarter, R. (2012). Spinal fusion in the United States: Analysis of trends from 1998-2008. *Spine, 37*, 67-76.

Rathod, T., Chandanwale, A., Gujrathi, S., Patil, V., Chavan, S. & Shah, M. (2012). Association between single nucleotide polymorphism in collagen IX and intervertebral disc disease in the Indian population. *Indian Journal of Orthopaedics, 46*, 420-426.

Redeker, N., Lev, E. & Ruggiero, J. (2000). Insomnia, fatigue, anxiety, depression and quality of life of cancer patients undergoing chemotherapy. *Scholarly Inquiry for Nursing Practice, 14*, 275-290.

Reishtein, J. (2005). Relationship between symptoms and functional performance in COPD. *Research in Nursing & Health, 28*, 39-47.

Rejeski, W.J. & Mihalko, S.L. (2001). Physical activity and quality of life in older adults. *Journals of Gerontology 56A,* 23-35.

Rihn, J., Kurd, M., Hilibrand, A., Lurie, J., Zhao, W., Albert, T. & Weinstein, J. (2013). The influence of obesity on the outcome of treatment of lumbar disc herniation. Analysis of the Spine Patient Outcomes Research Trial (SPORT). *The Journal of Bone and Joint Surgery, 95*, 1-8.

Rohan, M., Ohnmeiss, D., Guyer, R., Zigler, J., Blumenthal, S., Hochschuler, S., Sach, B., Rashbaum, R. (2009). Relationship between length of time off work preoperatively and clinical outcome at 24-month follow-up in patients undergoing total disc replacement or fusion. *The Spine Journal, 9*, 360-365.

Roland, M. & Fairbank, J. (2000). The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine, 25*, 3115-3124.

Rychnovsky, J. (2007). Postpartum fatigue in the active duty military woman. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 36*, 38-46.

Samartzis, D., Karppinen, J., Chan, D., Luk, K. & Cheung, K. (2012). The association of lumbar intervertebral disc degeneration on Magnetic Resonance Imaging with body mass index in overweight and obese adults. *Arthritis & Rheumatism, 64*, 1488-1496.

Samartzis, D., Karppinen, J., Mok, R., Fong, D., Luk, K. & Cheung, K. (2011). A population-based study of juvenile disc degeneration and its association with overweight and obesity, low back pain, and diminished functional status. *The Journal of Bone and Joint Surgery, 93*, 662-670.

Scott, J. & Huskisson, E. (1974). Graphic representation of pain. *Pain, 2*, 175-184.

Seki, S., Kawaguchi, Y., Mori, M., Mio, F., Chiba, K., Mikami, Y., Tsunoda, T., Kubo, T., Toyama, Y., Kimura, T. & Ikegawa, S. (2006). Association study of COL9A2 with lumbar disc disease in the Japanese population. *Journal of Human Genetics, 51,* 1063-1067.

Serlin, R., Mendoza, T., Nakamura, Y., Edwards, K. & Cleeland, C. (1995). When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain, 61,* 277-284.

Shiri, R., Karppinen, J., Leino-Arjas, P., Solovieva, S., & Viikari-Juntura, E. (2010). The association between obesity and low back pain: A meta-analysis. *American Journal of Epidemiology, 171*, 135-154.

Shiri, R., Karppinen, J., Leino-Arjas, P., Solovieva, S., & Viikari-Juntura, E. (2010). The association between smoking and low back pain: A meta-analysis. *The American Journal of Medicine, 123*, 87 .e7-87 .35.

Shiri, R., Solovieva, S., Husgafvel-Pursiainen, K., Taimela, S., Saarikoski, L., Huupponen, R., Viikari, J., Raitakari, L. & Viikari-Juntura, E. (2008). The association between obesity and the prevalence of low back pain in young adults: The Cardiovascular Risk in Young Finns study. *American Journal of Epidemiology, 167*, 1110-1119.

Sia, A., Lim, Y., Lim, E., Ocampo, C., Lim, W., Cheong, P. & Tan, E. (in press). Influence of mu-opioid receptor variant on morphine use and self-rated pain following abdominal hysterectomy. *The Journal of Pain*. Retrieved from http://www.sciencedirect.com.proxy1.cl.msu.edu/science/article/pii/S1526590013009395#

Siemionow, K., An, H., Masuda, K., Andersson, G. & Cs-Szabo, G. (2011). The effects of age, sex, ethnicity and spinal level on the rate of intervertebral disc degeneration a review of 1712 intervertebral discs. *Spine, 36*, 1333-1339.

Sigmundsson, F., Jonsson, B. & Stromqvist, B. (2013). Impact of pain on function and health related quality of life in lumbar spinal stenosis: A register study of 14.821 patients. *Spine, 38*, E937-E946.

Silverplats, K., Lind, B., Zoega, B., Halldin, K., Gellerstedt, M., Brisby, H. & Rutberg, L. (2010). Clinical factors of importance for outcome after lumbar disc herniation surgery: Long-term follow-up. *European Spine Journal, 19*, 1459-1467.

Slover, J., Abdu, W., Hanscom, B., Lurie, J. & Weinstein, J. (2006). Can condition-specific health surveys be specific to spine disease? An analysis of the effect of comorbidities on baseline condition-specific and general health survey scores. *Spine, 31*, 1265-1271.

Slover, J., Abdu, W., Hanscom, B. & Weinstein, J. (2006). The impact of comorbidities on the change in Short-Form-36 and Oswestry scores following lumbar spine surgery. *Spine, 31*, 1974-1980.

Smith, M., & Liehr, P. (2008). Understanding middle range theory by moving up and down the ladder of abstraction. In Smith, M. & Liehr, P. (Eds.), *Middle range theory for nursing.* (2nd Ed.). (pp. 13-31.). New York: Springer Publishing Company.

So, W., Leung, D., Ho, S., Lai, E., Sit, J. & Chan, C. (in press). Associations between social support, prevalent symptoms and health-related quality of life in Chinese women undergoing treatment for breast cancer: A cross-sectional study using structural equation

modeling. *European Journal of Oncology Nursing*. Retrieved from http//:dx.doi.org/10.1016/j.ejon.2012.11.001

Solovieva, S., Lohinvia, J., Leino-Arjas, P., Raininko, R., Luoma, K., Ala-Kokko, L. & Riihimaki, H. (2006). Intervertebral disc degeneration in relation to the *COL9A3* and *IL-1β* gene polymorphisms. *European Spine Journal, 15*, 613-619.

Solovieva, S., Noponen, N., Mannikko, M., Lein-Arjas, P., Luoma, K., Raininko, R., Ala-Kokko, L. & Riihimaki, H. (2007). Association between the aggrecan gene variable number of tandem repeats polymorphism and intervertebral disc degeneration. *Spine, 32*, 1700-1705.

Soysal, M., Kara, B. & Arda, N. (2012). Assessment of physical activity in patients with chronic low back or neck pain. *Turkish Neurosurgery, 23*, 75-80.

Tabachnick, B. & Fidell, L. (2007). *Using multivariate statistics* (5th Ed.). Boston: Pearson Education, Inc.

Takatalo, J., Karppinen, J., Taimela, S., Niinimaki, J., Laitinen, J., Sequeiros, B., Smartizis, D., Korpelainen, R., Nayha, S., Remes, J. & Tervonen, O. (2013). Association of abdominal obesity with lumbar disc degeneration—a magnetic resonance imaging study. *PLoS ONE, 8*, doi: 10.1371/journal.pone.0056244

Tarlov, A., Ware, J., Greenfield, S., Nelson, E., Perrin, E & Zubkoff, M. (1989). The Medical Outcomes Study: An application of methods for monitoring the results of medical care. *Journal of the American Medical Association, 262*, 925-930.

Taylor, C., Coxon, A., Watson, P. & Greenough, C. (in press). Do L5 and S1 nerve root compression produce radicular pain in a dermatomal pattern? Retrieved from http://ovidsp.tx.ovid.com.proxy2.cl.msu.edu/sp-3.12.0b/ovidweb.cgi?&S=BIMJFPNCDLDDNEAKNCMKFEDCJMIPAA00&Link+Set=jb.search.49%7c1%7csl_10

Taylor, S., Taylor, A., Foy, M. & Fogg, A. (1999). Responsiveness of common outcome measures for patients with low back pain. *Spine, 24*, 1805-1812.

Tetsunaga, T., Misawa, H., Tanaka, M., Sugimoto, Y., Tetsunaga, T., Takigawa, T. & Ozaki, T. (2013). The clinical manifestations of lumbar disease are correlated with self-rating depression scale scores. *Journal of Orthopaedic Science, 18*, 374-379.

Thomas, E., Silman, A., Croft, P., Papageorgiou, A., Jayson, M. & Macfarlane, G. (1999). Predicting who develops chronic low back pain in primary care: A prospective study. *BMJ, 318*, 1662-1667.

Trief, P., Grant, W. & Fredrickson, B. (2000). A prospective study of psychological predictors of lumbar surgery outcome. *Spine, 25*, 2616-2621.

Tsao, D., Shabalina, S., Gauthier, J,. Dokholyan, N. & Diatchenko, L. (2011). Disruptive mRNA folding increases translational efficiency catechol-O-methyltransferase variant. *Nucleic Acids Research, 39,* 6201-6212.

Tyler, R. & Pugh, L. (2009). Application of the Theory of Unpleasant Symptoms in bariatric surgery. *Bariatric Nursing and Surgical Patient Care, 4*, 271-276

U.S. Census Bureau, Statistical Abstract of the United States: 2012. (2012). *Resident Population Projections by Race, Hispanic-Origin Status, and Age: 2010 and 2015.* Retrieved from: http://www.census.gov/compendia/statab/2012/tables/12s0012.pdf

van Hooff, M., Spruit, M., O'Dowd, J., van Lankveld, W., Fairbank, J. & van Limbeek, J. (2013). Predictive factors for successful clinical outcome 1 year after an intensive combined physical and psychological programme for chronic low back pain. *European Spine Journal*, doi: 10.1007/s00586-013-2844-z

van Kleef, M., Vanelderen, P., Cohen, S., Lataster, A., Zundert, J. & Mekhail, N. (2010). Pain originating from the lumbar facet joints. *Pain Practice, 10*, 459-469.

Van Zundert, J., Vanelderen, P., Kessels, A. & van Kleef, M. (2012). Radiofrequency treatment of facet-related pain: Evidence and controversies. *Current Pain and Headache Reports, 16,* 19-25.

Varlotta, G., Lefkowitz, T., Schweitzer, M., Errico, T., Spivak, J., Bendo, J. & Rybak, L. (2011). The lumbar facet joint: A review of current knowledge: Part 1: Anatomy, biomechanics, and grading. *Skeletal Radiology, 40*, 13-23.

Verbrugge, L. & Jette, A. (1994). The disablement process. *Social Science & Medicine, 38*, 1-14.

Videman, T., Leppavuori, J., Kaprio, J., Battie, M., Gibbons, L., Peltonen, L. & Koskenvuo, M. (1998). Polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration. *Spine, 23*, 2477-2485.

Von Korff, M. & Saunders, K. (1996). The course of low back pain in primary care. *Spine, 21*, 2833-2839.

Voorhies, R., Jiang, X. & Thomas, N. (2007). Predicting outcome in the surgical treatment of lumbar radiculopathy using the Pain Drawing Score, McGill Short Form Pain Questionnaire, and risk factors including psychosocial issues and axial joint pain. *The Spine Journal, 7*, 516-524.

Vossen, H., Genis, G., Rutten, B., van Os., J., Hermanes, H. & Lusberg, R. (2010). The genetic influence on the cortical processing of experimental pain and the moderating effect of pain status. *PloS ONE, 5*, doi:10.1371/journal.pone.0013641

Wahlstrom, J., Burstrom, L., Nilsson, T. & Jarvholm, B. (2012). Risk factors for hospitalization due to lumbar disc disease. *Spine, 37*, 1334-1339.

Walsh, T., Hanscom, B., Lurie, J. & Weinstein, J. (2003). Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability Index, MODEMS, and the SF-36. *Spine, 28*, 607-615.

Ware, J., Kosinski, M., Bjorner, J., Turner-Bowker, D., Gandek, B. & Maruish, M. (2007). *User's Manual for the SF-36v2 Survey* (2nd Ed.). Quality Metric Incorporated.

Ware, J.E., Snow, K.K., Kosinski, M., & Gandek, B. (1993). *SF-36 Health Survey: Manual and Interpretation Guide.* Boston: Nimrod Press.

Ware, J. (2003). *SF-36 Health Survey Update*. Retrieved 11/22/2009 online from http://www.sf-36.org/tools/sf36shtml

Weinstein, J., Lurie, J., Olson, P., Bronner, K., & Fisher, E. (2006). Trends and regional variations in lumbar spine surgery: 1992-2003. *Spine, 31*, 2707-2714.

Werneke, M. & Hart, D. (2004). Categorizing patients with occupational low back pain by use of the Quebec Task Force classification system versus pain pattern classification procedures: Discriminant and predictive validity. *Physical Therapy, 84*, 243-254.

Werneke, M., Hart, D. & Cook, D. (2006). A descriptive study of the centralization phenomenon: A prospective analysis. *Spine, 24*, 676-683.

Wilson, H., Robinson, J., & Turk, D. (2009). Toward the identification of symptom patterns in people with fibromyalgia. *Arthritis & Rheumatism, 61*, 527-534.

Woods, S., Kozachik, S. & Hall, R. (2010). Subjective sleep quality in women experiencing intimate partner violence: Contributions of situational, psychological and physiological factors. *Journal of Traumatic Stress, 23*, 141-150.

World Health Organization (2002). *International Classification of Functioning, Disability and Health* (*ICF*). Retrieved from: http://www.who.int/classifications/icf/icfbeginnersguide.pdf?ua=1

Yang, Z., Lowe, A., de la Harpe, D. & Richardson, M. (2010). Pactors that predict poor outcomes in patients with traumatic vertebral body fractures. *Injury, 41*, 226-230.

Yorio, J., Yan, J., Xie, Y. & Gerber, D. (2012). Socioeconomic disparities in lung cancer treatment and outcomes persist within a single academic medical center. *Clinical Lung Cancer, 13*, 448-457.

Yuan, H., Tang, Y., Liang, Y., Lei, L., Xiao, B., Wang, S. & Xia, Z. (2010). Matrix metalloproteinase-3 and vitamin D receptor genetic polymorphisms and their interactions

with occupational exposure in lumbar disc degeneration. *Journal of Occupational Health, 52*, 23-30.

Zieger, M., Luppa, M., Meisel, H., Gunther, L., Winkler, D., Toussaint, R., Stengler, K., Angermeyer, M., Konig, H. & Riedel-Heller, S. (2011). The impact of psychiatric comorbidity on the return to work in patients undergoing herniated disc surgery. *Journal of Occupational Rehabilitation, 21*, 54-65.

Zhang, Y., Sun, Z., Liu, J. & Guo, X. (2008). Advances in susceptibility genetics of intervertebral degenerative disc disease. *International Journal of Biological Sciences, 4*, 283-290.

Zubieta, K., Heitzeg, M., Smith, Y., Bueller, J., Xu, K., Koeppe, R., Stohler, C. & Goldman, D. (2003). COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. *Science, 299*, 1240-1243.