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Relationship between Quality of Life for Patients with Neuroendocrine Tumors and Novel Biomarkers

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Walden University
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Abstract

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by

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MPH, Eastern Virginia Medical School, 2005

BS, The College of William & Mary, 2003

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Research in the field of neuroendocrine tumors (NETs) has increased over the last decade, including studies focused on biochemical markers (biomarkers) of the disease. There is also growing interest in how NETs impact patients' quality of life (QOL). Consequently, there is a paucity of information about whether the expression of the specific disease biomarkers affects QOL as well as whether the primary tumor site impacts QOL. Using the explanatory model of health promotion and quality of life in chronic disabling conditions as the theoretical framework and data collected with the Norfolk QOL-NET instrument, this study's purpose was to fill that gap in knowledge through research questions addressing the relationship between the primary tumor site and NET patients' total QOL score as well as the effect of specific NET biomarkers on NET patients' total QOL score. Data were analyzed using descriptive statistics, one-way analysis of variance (ANOVA), regression analysis, and post hoc tests to determine significance. Results from an ANOVA showed that abnormal NET biomarkers affected total QOL ($p = 0.011$). In the analyses of whether the independent biomarker variables affected the dependent total QOL variable, only the result for *Serotonin Normal* was significant ($p = 0.002$). The presence of abnormal biomarker measurements also affected two of the Norfolk QOL-NET domains significantly, gastrointestinal and physical functioning ($p = 0.005$ and $p = 0.030$, respectively). By understanding the relationship between NETs and patient QOL, the potential positive social change implications are helping NET patients assess the severity of their condition, determining what affects their well-being, and using this information to help monitor their treatment/progress.

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Dedication

This dissertation is dedicated to my husband, Michael, for all of his support over the years. It is also dedicated to my mother, Susan, for inspiring me to pursue and achieve my academic dreams. Finally, to my little Arthur James: you can do anything you set your mind to—it just takes perseverance.

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Chapter 1: Introduction to the Study

Introduction

Neuroendocrine tumors (NETs) have been referred to as a *Cinderella condition* because of the lack of recognition for this group of heterogeneous tumors (Vinik, Silva, & Vinik, 2011; Vinik, Vinik, Diebold, & Woltering, 2014). This lack of recognition persists, despite over 100,000 patients living with NETs in the United States and an increase in incidence over the last 30 years in the United States and Europe (Lawrence et al., 2011; Öberg, Knigge, Kwekkeboom, & Perren, 2012; Tsikitis, Wertheim, & Guerrero, 2012; Vinik, Carlton, Silva, & Vinik, 2009; Vinik et al., 2014). An increase in the incidence of NETs is also evident in Asian countries such as Japan and Korea (Hijioka et al., 2014; Lee et al., 2014). NETs develop in neuroendocrine cells throughout the body—they often progress slowly and are usually diagnosed after the tumors have metastasized (Haugland, Veenstra, Vatn, & Wahl, 2013; Mayo Clinic, 2013; Vinik et al., 2014). There are no known methods for the early detection or prevention of NETs (American Cancer Society [ACS], 2013; Öberg & Castellano, 2011; Tsikitis et al., 2012).

Research in the field of NETs has increased over the last decade, including an interest in biomarkers that have a role in disease diagnosis, prognosis, monitoring, and treatment (Ardill & Erikkson, 2003; Diebold et al., 2012; Modlin et al., 2008; Vinik et al., 2014). Biomarkers can be used to help distinguish among tumor types or act as a generic marker of NETs (Turaga & Kvols, 2011). There is increasing interest in how NETs influence QOL as well—this interest has resulted in the development of two disease-specific instruments. There is a body of research about the relationship between

biomarkers and NETs; however, there is very little information about whether the expression of the disease's novel biomarkers impacts patients' QOL. There is also a lack of information about whether a patient's primary tumor site affects QOL. This study was designed to fill those gaps. Results from this study could give physicians as well as patients and caregivers a better understanding of how the disease affects an individual's QOL. In turn, that information can be used to develop treatment options and programs to improve and maintain QOL for this patient population.

This chapter provides an overview of the research study. It includes background information about NETs along with a description of the research problem and how it addresses a gap in the research literature. The study's purpose, research questions, and hypothesis are also discussed. The theoretical framework, nature of the study, assumptions, scope/delimitations, and limitations are provided as well. The chapter concludes with an overview of the study's significance. More detailed information about existing research is discussed in Chapter 2.

Background

NETs were initially described in the mid- to late-19th century, and they continued to be defined through the present day (Hauso et al., 2007; Modlin et al., 2008; Öberg & Castellano, 2011; Turaga & Kvols, 2011; Van Eeden et al., 2002). Located throughout the body, neuroendocrine cells are similar to nerve cells and endocrine cells (ACS, 2013). This wide dispersion of cells contributes to the heterogeneity of NETs and the possibility of different primary tumor sites (e.g., appendix, colon, ileum, intestines, lungs, pancreas, or rectum; ACS, 2013; Mayo Clinic, 2013). The most common types of NETs are found

in the gastroenteropancreatic system and lungs (ACS, 2013; Diebold et al., 2012; Turaga & Kvols, 2011; Vinik et al., 2014). NETs lack definitive causative factors, but there are genetic and behavioral factors (such as smoking) associated with the disease's etiology (ACS, 2013; Tsikitis et al., 2012). For example, the MEN1 gene is associated with inherited and sporadic cases of NETs (ACS, 2013; Kulke et al., 2011; Metz & Jensen, 2008).

The tumors' heterogeneous nature, differences from other tumors found in the same organs, and lack of early detection methods make it difficult to diagnose and treat NETs: over 60% of cases are diagnosed at an advanced stage of disease (ACS, 2013; Jann et al., 2011; Modlin et al., 2008; Modlin et al., 2010; Turaga & Kvols, 2011; Van Eeden et al., 2002). The reason that the diagnosis is so challenging is partially due to the varying degrees of symptoms associated with the tumors. Some patients may exhibit many symptoms, whereas others may have no symptoms at all—it depends on whether or not the tumors overproduce certain regulatory hormones (Fröjd, Larsson, Lampic, & von Essen, 2007; Haugland et al., 2013; Kulke et al., 2011; Modlin et al., 2008). Tumor classification can also be complicated, and NET patients would benefit from an improved classification system (Jann et al., 2011). Furthermore, Öberg and Castellano (2011) stated that "…most patients lack access to the multidisciplinary early care necessary for optimal management of these complex tumors" (p. S3). A more in-depth discussion of NETs diagnosis, classification, and treatment is found in Chapter 2.

In addition to the lack of preventive methods for NETs, researchers have observed survival rate disparities related to anatomic locations of the tumor, geographic regions,

and race/ethnicity (ACS, 2013; Hauso et al., 2008; Lawrence, Gustafsson, Chan, et al., 2011; Modlin et al., 2008; Öberg et al., 2012; Tsikitis et al., 2012). It is estimated that there are five NET cases per 100,000 individuals in the United States annually, and the number of cases has increased over the last 30 years (ACS, 2013; Lawrence et al., 2011; Modlin et al., 2008; Vinik, Silva, & Vinik, 2011; Vinik et al., 2014). The prevalence is estimated at 35 cases per 100,000 individuals (Öberg & Castellano, 2011). Given the increase in incidence as well as the difficulties associated with prevention, diagnosis, and treatment, NETs are a potential public health issue.

There are known biomarkers associated with NETs (Ardill & Erikkson, 2003; Diebold et al., 2012; Modlin et al., 2008; Vinik et al., 2014). Each biomarker has its strengths and limitations. For example, Chromogranin A (CgA) is considered a general marker for NETs, but transcription factors CDX2 and TTF-1 are reliably used for midgut NETs and pulmonary NETs, respectively (Klöppel, 2007). Ito, Igarashi, and Jensen (2012), Lawrence et al. (2011), Modlin et al. (2010), as well as Öberg and Castellano (2011) highlighted a need for specific, high-quality biomarkers for early diagnosis, treatment, and disease management/follow-up. Biomarkers are addressed further in Chapter 2.

Research in the field of NETs has increased, as has an interest in patient-reported outcomes (Vinik et al., 2011; Vinik et al., 2014). This interest in patient-reported outcomes has been bolstered by the interest in making health a "patient-centered environment" and "…incorporating patients' assessments of their health status" in the field of medicine (Vinik et al., 2011, p. 99). The rise in patient-reported outcomes has led

to more interest in health-related QOL, a multidimensional concept that reflects all aspects of a patient's life that contribute to her health and well-being. Nonetheless, research about NETs and their impact on patients' QOL is limited (Vinik et al., 2011; Yadegarfar et al., 2013).

The Norfolk QOL-NET was developed as a NET-specific, health-related QOL tool in 2004 (E. Vinik et al., 2009; Vinik et al., 2014). This validated 72-item instrument can measure the "frequency and severity of symptoms" in addition to measuring eleven common symptoms of NETs (Vinik et al., 2011, p. 100). The Norfolk QOL-NET is comprised of seven different domains, and they are identified as follows: cardiovascular, depression, flushing, gastrointestinal, physical functioning, positive/negative attitude, and respiratory (E. Vinik et al., 2009). Physical functioning contributes the most to overall QOL (E. Vinik et al., 2009). Another validated NET-specific tool was developed in Europe, the EORTC QLQ-C30 QLQ-GINET-21 (Yadegafar et al., 2013). This tool is comprised of two parts: the generic, 30-item cancer questionnaire (EORTC QLQ-C30) and the 21-item, NET-specific QLQ-GINET-21 (Davies et al., 2006; Yadegarfar et al., 2013). Additional information about the EORTC QLQ-C30 QLQ-GINET-21 is found in Chapter 2. The secondary data analyzed in this study were collected with the Norfolk QOL-NET instrument.

As noted previously, a small body of literature about QOL and NET research exists. There is a need for more studies in this field because the findings could be used to benefit patients and their caregivers as well as facilitate improved disease management and patient care. Fröjd et al. (2007) found that NET patients had increased worries and

higher levels of emotional distress than the general population. Similarly, Haugland et al. (2009) observed that NET patients had impaired vitality and general health in addition to physical limitations. In another study, Haugland et al. (2013) showed that an intervention for NET patients helped improve QOL, particularly self-efficacy, physical functioning, and stress levels. Other studies examining QOL and NETs are reviewed in Chapter 2.

Notably, studies with the Norfolk QOL-NET have found correlations between tumor burden and three of the instrument's domains: physical functioning, depression, and gastrointestinal (Vinik et al., 2014). A significant correlation between serotonin (a biomarker for NETs), total QOL, and the three domains (physical functioning, depression, and gastrointestinal) was observed as well (Vinik et al., 2014). With the EORTC QLQ-C30 QLQ-GINET-21, Korse, Bonfrer, Aaronson, Hart, and Taal (2009) found that the universal NETs biomarker, CgA, was significantly correlated with physical functioning and overall QOL. CgA was associated with survival time as well (Korse et al., 2009). Combining studies about biomarkers with QOL could provide clinicians and researchers another avenue to further improve the diagnosis, treatment, and management of patients' disease.

Despite the abovementioned findings, there are gaps in the literature to be addressed. More research is warranted on the relationships between QOL (and aspects of QOL) and major NET biomarkers. Furthermore, given the disease's heterogeneity, there does not appear to be sufficient information about whether the primary tumor site has an impact on patients' QOL. Because these remain understudied areas of NET research, this study's results may make a contribution to the field by further exploring the relationship

between QOL and NETs. Per Vinik, E. et al. (2009), "consideration of a patient's QOL has become increasingly significant in evaluating the adverse health effects resulting from chronic illnesses such as NETs" (p. e87). Knowledge about NETs as they relate to patient QOL could make a positive social change by helping NET patients assess the severity of their condition, determine what's affecting their well-being, as well as help monitor their progress during treatment. Caregivers and physicians for NET patients can also benefit from this information. QOL information can connect physicians with their patients and give them a better understanding of what's influencing their outcomes.

Problem Statement

While other studies have shown that NET patients have diminished QOL when compared to a general population, there are still unknowns about the relationship between the overall QOL of NET patients and their primary tumor sites (Fröjd et al., 2007; Haugland et al., 2009; Knox et al., 2004; Larsson, Sjödén, Öberg, Eriksson, & von Essen, 2001; E. Vinik et al., 2009; Vinik et al., 2011; Vinik et al., 2014; Yadegarfar et al., 2013). Some researchers' studies have evaluated the association between QOL and certain NET biomarkers; however, most of these studies focused on CgA, 5-hydroxyindoleacetic acid (5-HIAA), and serotonin (Korse et al., 2009; Larsson et al., 2001; Vinik et al., 2011; Vinik et al., 2014). It is likely that the presence of specific biomarkers associated with NET-related symptoms or tumor types negatively impacts patients' QOL or even aspects of QOL (like the cardiovascular or flushing domains in the Norfolk QOL-NET); furthermore, different primary tumor types may have varying effects on QOL (ACS, 2013; Lawrence, Gustafsson, Kidd, et al., 2011; Haugland et al., 2013; Modlin et al.,

2008; Vinik & Gonzales, 2011). As mentioned in previous publications, QOL acts as the dependent variable that changes based on other factors (Stuifbergen, Seraphine, & Roberts, 2000). This study was devised to move beyond what has been published by examining the relationship between total QOL and patients' primary tumor sites. Additionally, the relationship between total QOL and six novel biomarkers of NETs (5-HIAA, CgA, gastrin, Neurokinin A [NKA], pancreastatin, and serotonin) was investigated. This study was designed to address gaps in the research literature about the impact of NET biomarkers as well as whether the primary tumor site affects patients' QOL.

Purpose

The purpose of this quantitative study was to determine whether there was an association between the total QOL (dependent variable) of NET patients and their different primary tumor sites (independent variable). The relationship between QOL and disease-specific biomarkers was also assessed. The biomarkers were assessed as independent variables to determine whether they affect QOL.

Research Questions and Hypotheses

The research questions and hypotheses for this study were as follows:

Research Question 1: What is the relationship between the primary tumor site and NET patients' total QOL score?

$H_0$1: There is no relationship between the primary tumor site and NET patients' total QOL score.

$H_1$1: There is a relationship between the primary tumor site and NET patients' total QOL score.

Research Question 2: How does the presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affect the total QOL score for NET patients?

$H_0$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) does not affect the total QOL score for NET patients.

$H_1$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affects the total QOL score for NET patients.

Theoretical Framework

Explanatory theory, specifically the explanatory model of health promotion and quality of life in chronic disabling conditions, was used as this study's theoretical framework. The National Cancer Institute (NCI, 2005) stated that explanatory theory "…guides the search for factors that contribute to a problem" (p. 5). Through explanatory theory, the components of a disease or health problem can be identified and later applied to health interventions; similarly, QOL is a patient-reported outcome that is comprised of multiple measureable domains (or components) such as social well-being and physical functioning (Green, 2000; NCI, 2005; Vinik et al., 2014). Kleinman, Eisenberg, and Good (1978) developed an explanatory model that underscored the importance of the way people understand their illness and health-related experiences. Comparable to QOL, Kleinman et al.'s (1978) explanatory model is concerned with patient-reported perceptions of illness or health. Like explanatory theory, QOL seeks to answer the *how*

and *why* aspects of a disease from the patient's point of view. A QOL study based on this theoretical framework could help increase one's understanding about how a disease or condition impacts patients.

Stuifbergen et al. (2000) developed the explanatory model of health promotion and quality of life in chronic disabling conditions. In this model, like the proposed study, QOL was the dependent variable affected by different factors (e.g., behavioral, contextual, and/or attitudinal) either directly or indirectly (Stuifbergen et al., 2000). This explanatory model identified three variables (health-promoting behaviors, severity of illness, and resources) that directly impact QOL (Stuifbergen et al., 2000). It was reflective of the proposed study's research questions into the effects of NET biomarkers and primary tumor sites on the dependent variable of QOL. Furthermore, a health-related QOL study that applied this framework could be considered the first step toward identifying factors that could be modified to help improve QOL in future studies for NET patients.

Nature of the Study

In this quantitative study, I analyzed secondary, de-identified clinical data that were collected from NET patients using the Norfolk QOL-NET questionnaire. The Norfolk QOL-NET is a validated and reliable 72-item questionnaire that measures seven domains that impact the QOL of NET patients (E. Vinik et al., 2009; Vinik et al., 2011). The study data were quantitative, cross-sectional, and generalizable to a NET patient population in the same age range as the patients in the dataset. A quantitative approach aligned with the analysis of the questionnaire-based numerical data and the problem

statement. Data for Research Question 1 and Research Question 2 were analyzed via a one-way analysis of variance (ANOVA) test and a post hoc test. The biomarkers and primary tumor sites were evaluated as independent variables to determine their relationship with total QOL scores. Total QOL was the dependent variable. Data were also evaluated using multiple linear regression analysis for Research Question 1 and Research Question 2.

Operational Definitions of Technical Terms

Quality of life or *QOL*: The overall concept of *health-related quality of life* unless stated otherwise. The concept of QOL was revised to incorporate health by the World Health Organization (WHO) after World War II (Centers for Disease Control and Prevention [CDC], 2011; Ormel, Lindenberg, Steverink, & Vonkorff, 1997; Vinik et al., 2011; Vinik et al., 2014). QOL is multidimensional, reflecting patients' well-being as well as the ways that their life experiences and illness/health conditions impact their daily lives (CDC, 2011; E. Vinik et al., 2009).

Primary tumor site: Where the cancer originated in the body (ACS, 2013).

Biomarker: The measureable hormones and peptides that are used to help diagnose the disease and/or identify the type of tumor as well as help determine whether a treatment is working or the tumor has recurred (Diebold et al., 2012; Eriksson, Öberg, & Stridsberg, 2000). A biomarker may be prognostic or predictive (Eriksson et al., 2000). Some of the NETs biomarkers are also associated with survival (Diebold et al., 2012).

Immunohistochemistry: An analytical technique used to test for certain molecules (e.g., biomarkers) in tissues (NCI, n.d.).

Neuroendocrine cells: Part of the body's diffuse neuroendocrine system. These cells behave "…like nerve cells in certain ways and like hormone-making endocrine cells in other ways" (ACS, 2013, p. 3). These cells regulate gut motility and are the body's largest group of hormone-secreting cells (Lawrence, Gustafsson, Chan, et al., 2011; Modlin et al., 2008).

Gastroenteropancreatic system: The anatomical sites where these tumors commonly arise in the gastrointestinal tract and pancreas, including the following: the foregut (first duodenum, stomach, bronchi, and thymus); midgut (appendix, right colon, ileum, second duodenum, and jejunum); hindgut (from the transverse colon to the rectum); and the pancreas (Turaga & Kvols, 2011).

Assumptions

Assumptions were necessary for the identification of potential threats to the study's validity. Given that secondary data from a questionnaire were used for this study, it was assumed that the patients who responded to the Norfolk QOL-NET answered the questions honestly. It was assumed that the QOL data, primary tumor information, and biomarker data were recorded accurately in the database. It was also assumed that QOL data were collected and coded properly.

Scope and Delimitations

Based on other studies in the literature, it was believed that NETs and their related biomarkers affected patients' QOL. This study was conceived to fill a gap in knowledge about the relationship between NET biomarkers, primary tumor sites, and QOL. The secondary data were originally collected from NET patients using a validated and reliable

NET-specific instrument. Participants were selected because they were NET patients. Consequently, these study data were limited to adult patients with NETs ranging from 18 to 85 years of age, so the results were not generalizable to any other patient population. I considered health belief theory and social cognitive theory, but they did not seem to fit the multiple domain, component-like aspect of QOL like explanatory theory and the explanatory model of health promotion and quality of life in chronic disabling conditions. As such, they were not used in the study.

Limitations

Analytically, it was assumed that the data were normally distributed within the independent variable, had equal variances, and were independent. As with any questionnaire-related study, there was also concern about self-report or recall bias affecting the results. The Norfolk QOL-NET's reliability and validity helped avoid instrumentation limitations. Significant findings from this study population, discussed in Chapters 4 and 5, warrant future research in a larger study population. The differences in the interpretation between age groups may be a limitation and are discussed further in Chapter 5 with the interpretation of the results.

Significance of the Study

Patient-reported outcomes are important to evaluate in clinical studies (Vinik et al., 2011; Yadegarfar et al., 2013). This study determined whether tumor sites and biomarkers affected QOL, which may facilitate a better understanding of the disease and its relationship to patient-reported outcomes; ultimately, this information could contribute to positive social change in the field. This study could be one of the first to demonstrate

an association between novel biomarkers for NETs (other than serotonin) and QOL. This information could benefit professional practice by influencing decision-making approaches to treatments for NETs over time. Additionally, results from studies that use instruments such as the Norfolk QOL-NET could be used to develop interventions or patient education programs that can reduce the effects of symptoms and disease-related stress as well as improve self-efficacy, physical functioning, and total QOL for this population (Haugland et al., 2013). These types of interventions could have a significant positive impact on the NET patient population and their caregivers.

Summary

The field of NET research is growing, leading to a deeper understanding of this heterogeneous disease and its biomarkers. Researchers have shown that NET biomarkers can have a unique impact on the disease, from its presentation to symptom manifestation and even disease survival (Ardill & Erikkson, 2003; Diebold et al., 2012; Ito et al., 2012; Lawrence, Gustaffson, Kidd, et al., 2011; Modlin et al., 2008; Modlin et al., 2010; Öberg & Castellano, 2011; Turaga & Kvols, 2011; Vinik et al., 2014). There is also an increased interest in NETs and QOL—this research could further the understanding of various factors that impact patients' QOL. Despite the growing interest in the topic, there is still a need for additional studies that delve further into how NETs affect patients' QOL. In this study, I aimed to fill that gap by determining whether there was a relationship between QOL and different primary tumor sites. I also investigated the relationship between novel, disease-specific biomarkers and QOL for patients with NETs. Ultimately,

combining aspects of QOL research with tumor-specific research could help provide a more complete picture of the disease and its impact on patients.

Chapter 2 includes an overview of the literature relevant to this research, including information about the study framework, NETs, NET-related biomarkers, as well as NETs and QOL. In Chapter 3, I address this study's research design, the Norfolk QOL-NET instrument, and statistical analyses. Chapter 4 includes the results from the analyses as they pertain to the research questions and hypotheses. In Chapter 5, I present an interpretation of the study's findings along with implications for social change and recommendations for action/future studies.

Chapter 2: Literature Review

Introduction

The purpose of this study was to examine the relationship between total QOL and patients' primary tumor sites. Additionally, the relationship between total QOL and six novel biomarkers of NETs (5-HIAA, CgA, gastrin, NKA, pancreastatin, and serotonin) was investigated. This literature review affirmed the need to address the unknowns about the relationship between the QOL of NET patients with different primary tumor sites and six novel biomarkers of the disease. While research about NETs and interest in patient-reported outcomes have increased over the last decade, QOL as it relates to this type of cancer is a young field (Vinik et al., 2011; Yadegarfar et al., 2013). Results from the literature review demonstrated that the body of literature about QOL and NETs is not extensive. It further emphasized the gap of knowledge about QOL, NETs, and biomarkers in this field. Although there is substantial information about established NET facts in the literature, there are still many unknowns (including the molecular mechanisms of this heterogeneous disease and the role of certain biomarkers). Modlin et al. (2008) commented that the field of NETs is underfunded, which likely contributes to the smaller body of research. Given that the field of NET research is growing, results from this study could potentially make a noteworthy contribution to the field.

This chapter includes an overview of NETs, including primary tumor sites, epidemiology, biomarkers, and their relationship to the disease. A discussion of QOL as it relates to NETs is also included. The Norfolk QOL-NET as well as the European NET-specific instrument, the EORTC QLQ-C30 QLQ-GINET21, are also described in this

chapter. A summary of QOL and NET research studies that used either generic or disease-specific instruments is presented. The literature search strategy is discussed along with the theoretical framework (explanatory model of health promotion and quality of life in chronic disabling conditions) and its relationship to this study as well.

Literature Search Strategy

For this research, a literature search was conducted online using electronic databases including PubMed, Google Scholar, Google, and Walden University's library. For the chapter's theoretical framework section, search terms included *explanatory theory* with *origin*, *definition*, *health*, *quantitative study*, *quality of life*, or *health model*. Other search terms included *neuroendocrine tumors* along with one of the following: *QOL*, *QOL-NET*, *EORTC QLQ-GINET21*, *NKA*, *pancreastatin*, *serotonin*, *5-HIAA*, *gastrin*, and *CgA*. All of the peer reviewed articles and book chapters were obtained digitally. The scope of literature ranged from 1978 to the present. Older peer reviewed sources were used for historical content, while peer reviewed sources published within the last decade were used as the focus of the literature review. Two books were used as sources because they contained relevant information about biochemical measures and NETs. Peer reviewed sources were selected based on their relevance to the proposed study.

Theoretical Framework

The theoretical framework applied to this research was explanatory theory, specifically the explanatory model of health promotion and quality of life in chronic disabling conditions. Explanatory theory's foundation is in factors that determine health

and health behaviors—as a theory, it can help investigators answer the *why* questions of health problems (Green, 2000; NCI, 2005). Other theories in health promotion are considered explanatory theories, including the theory of planned behavior and the health belief model (NCI, 2005). Explanatory theory allows for the identification of a disease or problem's components that could be addressed by future interventions (Green, 2000; NCI, 2005). Similarly, health-related QOL is a patient-reported outcome comprised of multiple measurable domains (e.g., physical and psychological functioning), and knowledge about patient-reported QOL can help determine what factors need to be addressed to improve one's health and well-being (Vinik et al., 2014). Explanatory theory has been applied to QOL-related research before, but not as it relates to NET studies. It is, however, supportive of the multidimensional concept of health-related QOL.

Patient-reported QOL is a multidimensional construct (Cummins, 2005; Vinik et al., 2011; Vinik et al., 2014). As such, it is well-suited to an explanatory theory-related framework because it looks at components that help answer the *how*, *why*, and *what* factors of a condition or disease from the patient perspective. A QOL study rooted in this theoretical framework can help increase one's understanding about how a disease or condition impacts patients. Furthermore, a health-related QOL study that applied an explanatory theory as a framework could be considered the first step toward identifying factors that could be modified to improve health-related QOL in future studies.

Some investigators used explanatory theory to develop explanatory models. One of these models is Kleinman et al.'s (1978) explanatory model of illness. It is an important model that describes how people understand their illness and related

experiences (Kleinman et al., 1978). Much like QOL, the explanatory model of illness is comprised of patient-reported perceptions of their health/illness. Explanatory theory itself has not been widely applied to QOL research, but there are studies that incorporate these concepts. Cummins (2005) identified a need for a testable theory for QOL and proposed that conceptual models of QOL (with indicator and causal variables) could transition to explanatory theory.

Stuifbergen et al. (2000) developed an explanatory model of QOL based on findings from quantitative and qualitative studies in the literature. In their explanatory model, they determined that QOL is shaped directly and indirectly by different factors (e.g., behavioral, contextual, and/or attitudinal; Stuifbergen et al., 2000). This model also assumes that QOL changes over time along with an individual's illness or health status (Stuifbergen et al., 2000). In this model, like this study, QOL is the dependent variable affected by other independent variables (Stuifbergen et al., 2000). Additionally, this explanatory model identifies three variables (health-promoting behaviors, severity of illness, and resources) that directly impact QOL (Stuifbergen et al., 2000). Results from a study in a large population with multiple sclerosis supported Stuifbergen et al.'s (2000) explanatory model of QOL, and the authors observed that the factors that impact QOL would be useful targets for interventions for a population with a chronic disabling condition. Phillips' (2005) analysis of Stuifbergen et al.'s (2000) model concluded that it is valuable "…to expand the knowledge base of nurses and other professionals" as well as to help patients with chronic conditions (p. 22). This model is appropriate because it

mirrored the proposed study's research questions that evaluated the effects of NET biomarkers and primary tumor sites on the QOL of NET patients.

Neuroendocrine Tumors

Neuroendocrine Tumors and their Primary Tumor Sites

The first NETs were identified at different points in the latter half of the 19th century by three pathologists: Theodor Langhans, Otto Lurbarsch, and William Ransom (Hauso et al., 2007; Öberg & Castellano, 2011). These tumors were further described in the early 1900s by Siegfried Oberndorfer—he coined the term *karzinoide* in 1907 and later defined malignant NETs in 1929 (Modlin et al., 2008; Turaga & Kvols, 2011; Van Eeden et al., 2002). Pierre Masson and Andre Gosset elaborated on the endocrine nature of *carcinoid tumors* in 1914 (Hauso et al., 2008; Van Eeden et al., 2002).

NETs are rare, slow progressing, heterogeneous tumors that arise in cells in the body's widely-dispersed neuroendocrine system or diffuse endocrine system (ACS, 2013; Haugland et al., 2013; Klöppel, 2007; Öberg, Knigge, Kwekkeboom, & Perren, 2012; Prestifilippo, Blanco, Vitalo, & Giuffrida, 2012; Tsikitis et al., 2012; Vinik et al., 2014). ACS (2013) noted that these cells exhibit similarities to hormone-producing endocrine cells as well as nerve cells and can be found throughout the body. According to Modlin et al. (2008), neuroendocrine cells are "…the largest group of hormone-producing cells in the body" (p. 62). This wide-dispersion is the reason why there are multiple primary tumor sites for this type of cancer. NETs can be found throughout the body, particularly in the pancreas, gastrointestinal system (appendix, intestines, ileum, stomach, colon, and rectum), and lungs (ACS, 2013; Mayo Clinic, 2013; Vinik et al., 2014). In the

gastroenteropancreatic system, NETs are more common in the small intestine, especially the ileum (ACS, 2013; Diebold et al., 2012; Turaga & Kvols, 2011). They are also common in the jejunum (Diebold et al., 2012).

Causes of NETs. The causes of NETs are still unknown. Some inherited and sporadic cases of NETs are related to mutations in the MEN1 gene (ACS, 2013; Kulke et al., 2011). Over 80% of patients with MEN1 mutations will develop pancreatic NETs (Metz & Jensen, 2008). It has been estimated that 10% of gastrointestinal NETs are the result of an inherited mutation in the MEN1 gene (ACS, 2013). There are also inherited cases of NETs in the small intestines that are related to mutations in the NF1 gene (ACS, 2013; Kulke et al., 2011). Pernicious anemia and low acid states are associated with type 1 gastric carcinoids (Lawrence, Gustafsson, Chan, et al., 2011). Individuals with von Hippel-Lindau syndrome (VHL) and tuberous sclerosis complex (TSC) are at an increased risk for NETs as well (ACS, 2013; Öberg et al., 2012; Kulke et al., 2011). A different mutation in the VHL gene has been related to VHL-associated gastroenteropancreatic NETs (Turaga & Kvols, 2011). Metz and Jensen (2008) reported that individuals with MEN1 disorder, VHL, TSC, or NF1 have an increased incidence of developing pancreatic NETs. Approximately 11%-17% of individuals with VHL will develop a pancreatic NET (Turaga & Kvols, 2011).

The majority of NET cases appear to occur because of sporadic mutations in tumor suppressor genes or oncogenes; nonetheless, there are insufficient data about neuroendocrine tumorigenesis (ACS, 2013; Metz & Jensen, 2008; Modlin et al., 2008; Turaga & Kvols, 2011). Modlin et al. (2008) observed that preclinical studies related to

NET pathogenesis (e.g., in cell lines and animal models) "…have had substantial limitations" and "…have not successfully translated to the clinic" (p. 63). There have been rodent studies with promising results, but a lack of genomic information limited them (Modlin et al., 2008). There is also a dearth of human neuroendocrine cell lines (Modlin et al., 2008). Research on deoxyribonucleic acid (DNA) microarrays for NET gene expression profiles is underway, but nothing has been validated yet (Turaga & Kvols, 2011).

Diagnosis, classification, and treatment. The tumors' heterogeneous nature makes them a challenge to diagnose and treat (Jann et al., 2011). NETs are different from other types of tumors found in the same organs, and there are no methods for early detection (ACS, 2013; Öberg & Castellano, 2011). As such, delayed diagnosis after the tumors have metastasized is common—it is estimated that 60%-80% of patients have metastatic NETs when diagnosed (Modlin et al., 2008; Modlin et al., 2010; Turaga & Kvols, 2011; Van Eeden et al., 2002). Sometimes, diagnosis can be delayed as long as 5-7 years or more (Modlin et al., 2008; Öberg & Castellano, 2011). Survival increases if diagnosis occurs prior to metastases, highlighting the need for more sensitive and specific imaging techniques as well as the development of new biomarker assays to better diagnose NETs (Öberg & Castellano, 2011; Vinik et al., 2011).

NETs may be considered functional (meaning that they actively secrete hormones or peptides) or nonfunctional. Functional tumors are usually diagnosed before nonfunctional cases because of the related symptoms. Different imaging modalities (e.g., positron emission tomography scan, computerized tomography scan, or MRI) may be

used to help diagnose the cause of symptoms (ACS, 2013; Öberg & Castellano, 2011). NETs may also be detected by endoscopy, colonoscopy, blood/urine tests for certain biomarkers, or biopsies, depending on the symptoms, clinical suspicions, and/or the clinician (ACS, 2013; Öberg & Castellano, 2011). NET-related symptoms are the result of the overproduction of regulatory hormones, amines, or vasoactive peptides secreted by the tumors, and they can differ on a case by case basis (Haugland et al., 2013; Kulke et al., 2011; Modlin et al., 2008; Öberg & Castellano, 2011). Individuals can be completely asymptomatic, indicating that their tumor is probably nonfunctional, whereas others may have functional tumors that secrete hormones or peptides, causing severe symptoms (ACS, 2013; Haugland et al., 2013; Modlin et al., 2008). Symptoms such as diarrhea, flushing, and wheezing are related to hormones released by the tumors (ACS, 2013; Haugland et al., 2013). Some of the hormones released by certain NETs can damage the heart and result in carcinoid heart disease (ACS, 2013). Dobson et al. (2013) observed that carcinoid heart disease "…has prognostic significance for long-term survival" (para. 3). A combination of certain symptoms in NET patients (diarrhea, flushing, and heart disease) is referred to as carcinoid syndrome (Öberg & Castellano, 2011). Other clinical syndromes can result from the expression of these substances, including Verner Morrison syndrome (vasoactive intestinal peptidoma), Zollinger-Ellison syndrome (ZES; gastrinoma), hypoglycemia, and WDHA syndrome (watery diarrhea hypokalemia, and achlorhydria; Öberg & Castellano, 2011). These hormones and peptides are considered biomarkers of the disease—they are discussed later in the chapter.

Classification of NETs is complicated and difficult; yet, it can be critical for patients' disease management and survival. Despite the clinicopathological heterogeneity of the tumors, there are physical similarities that result in them being grouped together, such as cell structure and secretory granules (Öberg & Castellano, 2011; Prestifilippo et al., 2012). For example, pancreatic NETs share similar features with gastrointestinal NETs, but there are distinct differences in the diagnosis, management/treatment, and proposed pathogenesis of the tumors (Metz & Jensen, 2008).

Gastroenteropancreatic NETs were divided into hindgut (rectum and colon), midgut (appendix, caecum, distal duodenum, ileum, and jejunum), and foregut (proximal duodenum, liver, pancreas, stomach, and upper jejunum) classifications in 1963 (Klöppel, 2007; Öberg & Castellano, 2011). These classifications are still applicable today. They are also categorized as "poorly differentiated neuroendocrine carcinomas" or "well-differentiated neuroendocrine tumors" (Klöppel, 2007, p.15). Of the gastroenteropancreatic NETs, those of the midgut are the most common, presenting with vague symptoms that have delayed diagnosis for up to 10 years (Diebold et al., 2012). NETs of the lung are either referred to as "small/large-cell neuroendocrine carcinomas" or "carcinoid" (Klöppel, 2007, p. 15). Additionally, "…moderately differentiated neuroendocrine tumors in the stomach, intestine, appendix, rectum, and lung" may be described as "carcinoid tumors" (ACS, 2013, p. 4). There are subtypes within each organ-specific type of NET as well (Klöppel, 2007).

Improving tumor classification so it is a prognostically valuable process would be beneficial for NET patients (Jann et al., 2011). Previously, tumors were staged based on

metastases only: local, regional, and distant (ACS, 2013). More recently, staging is done using the American Joint Committee on Cancer's tumor-node-metastasis (TNM) system (ACS, 2013). Staging is completed using information about the tumor's size, the amount the tumor spread to regional lymph nodes, and metastases to other organs (ACS, 2013). There are additional details measured within each level of TNM (ACS, 2013). Related, Jann et al. (2011) noted that staging NETs using the European NET Society's (ENETS) proposed TNM classification system "…was a valid predictor of long-term outcome" for patients and has "…predictive value for the prognostic stratification of these patients" (p. 3333). The ENETs-TNM system incorporates metastatic disease, tumor size/thickness, and lymph node involvement (Turaga & Kvols, 2011). Jann et al. (2011) conducted one of the first validation studies of the ENETS-TNM system in a European population of 270 patients with gastroenteropancreatic NETs (primary tumors in the midgut and hindgut). Results showed that the ENETS-TNM classification system was valid for the prognostic stratification of the study population's NETs (Jann et al., 2011). This classification system discriminated between local, locoregional, and advanced stage disease in a prognostically relevant, statistically significant manner (Jann et al., 2011).

The WHO published an updated classification of NETs in 2000, 2004, and 2010 (Öberg & Castellano, 2011). The WHO classification divides the tumors into well-differentiated NETs, well-differentiated neuroendocrine carcinomas, and poorly differentiated neuroendocrine carcinomas (Öberg & Castellano, 2011). Öberg and Castellano (2011) stated that "although the new WHO classification is an important step towards defining the diverse tumor biology of NETs, further efforts are necessary to

improve the prognostic assessment of each individual NET" (p. S4). This classification system was described as favored by clinicians, but also "time-consuming" because of the pathological examination required for the diagnosis (Öberg & Castellano, 2011).

Currently, treatment is based on a patient's symptoms and tumor burden (Modlin et al., 2008). Modlin et al. (2008) stated that "the best therapeutic choice for individual patients will depend on whether the main aim of treatment is to slow tumour growth or ameliorate symptoms by inhibition of the secretion of bioactive agents" (p. 67). The primary NET treatments include surgery, chemotherapy (e.g., cisplatin, doxorubicin, 5-fluorouracil, capecitabine, or etoposide), and radiation (ACS, 2013; Modlin et al., 2008). Ablation or embolization may be an option for patients with tumors that have metastasized to their livers (ACS, 2013). Surgery can prolong survival and may be curative for patients with early stage tumors (Kulke et al., 2011; Modlin et al., 2008). Although surgery may prolong survival for patients with advanced disease, other NET-related complications (such as hormone secretion) can contribute to patient's mortality (Kulke et al., 2011). Furthermore, chemotherapy drugs are not always effective for NET patients, emphasizing the need for more targeted treatments for this heterogeneous disease (Modlin et al., 2008). New therapies, like peptide receptor radiotherapy, are being evaluated (Kulke et al., 2011). Kulke et al. (2011) mentioned that clinical trial design can be challenging because of the "unique characteristics" presented by NETs; however, some promising treatments exist and are being evaluated, including mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogs, vascular endothelial growth factor (VEGF) pathway inhibitors, and temozolomide (p. 938).

Risk Factors and Epidemiology

While there is a lack of causative factors for NETs, researchers have identified risk factors for this heterogeneous disease, including genetic markers (discussed previously), age (older than 60 years of age), smoking, and race (African American; ACS, 2013; Tsikitis et al., 2012). For unknown reasons, these tumors also appear to be more common in women than men in the United States (ACS, 2013). Of note, NET data from Europe showed that men have a slightly higher incidence of NETs than women (Öberg et al., 2012). With regards to NETs, Lawrence, Gustafsson, Chan, et al.'s (2011) noted that "there is a distinct epidemiologic profile for each primary site" (p. 16).

The incidence of NETs in the United States has increased over the last 30 years, but it is unclear why this is happening (ACS, 2013; Lawrence, Gustafsson, Chan, et al., 2011; Modlin et al., 2008; Tsikitis et al., 2012). The increase in incidence could have occurred because of greater disease awareness, more diagnostic scans for other issues (such as colonoscopies and endoscopies), improved immunohistochemical serodiagnostic testing, or the actual occurrence of more cases (ACS, 2013; Hauso et al., 2008; Lawrence, Gustafsson, Chan, et al., 2011; Modlin et al., 2008). In Caucasian and African American populations in the United States, Modlin et al. (2008) reported a 460% and 720% increase (respectively) in NET incidence over a 30-year period. Currently, it is estimated that there are 5 NET cases per 100,000 individuals in the United States annually (Vinik et al., 2011; Vinik et al., 2014). The prevalence is estimated at 35 cases per 100,000 individuals (Öberg & Castellano, 2011). Lawrence, Gustafsson, Chan, et al. (2011) pointed out that gastroenteropancreatic NETs have a higher prevalence "…than

that of most gastrointestinal cancers, including pancreatic, gastric, esophageal, and hepatobiliary carcinomas, and is only exceeded by that of colorectal neoplasia" (p. 1).

Lawrence, Gustafsson, Chan, et al.'s (2011) epidemiologic study analyzed Surveillance, Epidemiology and End Results (SEER) data (1973-2007) from 49,012 patients with NETs. They also found an increase in the incidence of NETs, particularly gastroenteropancreatic NETs (Lawrence, Gustafsson, Chan, et al., 2011). Their study found a notable increase in small intestinal and rectal NETs (Lawrence Gustafsson, Chan, et al., 2011). Other studies, like Tsikitis et al. (2012), had similar results. Lawrence, Gustafsson, Chan, et al. (2011) observed that it is likely that the increase in endoscopies and other diagnostic modalities (e.g., colonoscopies) has contributed to the growing incidence rates.

In a retrospective analysis, Tsikitis et al. (2012) examined trends in the incidence and survival of gastrointestinal NETs in the United States (from 1973-2008) using data on 19,669 individuals from the SEER database. Notably, over the 35-year time period, NETs in all gastrointestinal sites (except the appendix) increased significantly across all regions of the United States (Tsikitis et al., 2012). In their study, the authors found that most of the tumors arose in the small intestine (n = 7,181) and rectum (n = 6,796) than other sites (Tsikitis et al., 2012). Women had significantly higher rates of NETs in the colon, appendix, and stomach than men (Tsikitis et al., 2012). Tsikitis et al. (2012) also found that NETs in the colon, small intestine, and stomach were significantly more common in individuals older than 60 years of age than NETs in the rectum and appendix. They also found a racial disparity in the incidence of NETs in the rectum (Tsikitis et al.,

2012). Of note, individuals whose primary tumor site was the appendix or rectum appeared to have a better prognosis than others (Tsikitis et al., 2012). Their analysis of survival data showed that patients with NETs in the rectum or appendix had the best survival rates as well (Tsikitis et al., 2012).

In another study, Hauso et al. (2008) compared NET data (1993-2004) from the SEER database and Norwegian Registry of Cancer (NRC) to ascertain whether there was a difference in disease epidemiology on a global scale. Given the primarily Caucasian population of Norway, the subset of SEER data on Caucasian NET patients was compared to Norwegian NET patients (Hauso et al., 2008). Separately, the researchers compared the SEER Caucasian and African American NET patients over the same timeframe (Hauso et al., 2008). Results from this study showed that Caucasians from the SEER database had a 37% higher incidence rate of NETs than those from the NRC, largely due to higher rates of bronchopulmonary and rectal NETs in the United States (Hauso et al., 2008). However, the overall incidence rate of NETs was found to be increasing faster in Norway than the United States (Hauso et al., 2008). Hauso et al. (2008) also confirmed that there is a higher incidence of NETs in African Americans in the United States than Caucasians. In particular, African Americans had significantly higher incidence rates of rectal and small intestinal NETs than Caucasians (Hauso et al., 2008).

The 5-year survival rates for NET patients vary, depending on the primary tumor type and the extent of metastases. These rates do not appear to have improved much for gastroenteropancreatic NETs (Lawrence, Gustafsson, Chan, et al., 2011). ACS (2013)

listed the 5-year survival rates (1988-2004) for gastrointestinal NETs in the United States as follows: 73% (localized) to 25% (distant metastases) for stomach NETs; 68% (localized) to 46% (distant metastases) for duodenum NETs; 65% (localized) to 54% (distant metastases) for jejunum/ileum NETs; 88% (localized) to 25% (distant metastases) for appendix NETs; 85% (localized) to 14% (distant metastases) for colon NETs; and 90% (localized) to 24% (distant metastases) for rectal NETs. Turaga and Kvols (2011) as well as Modlin et al. (2008) reported that the overall 5-year survival rate for small intestinal carcinoids is 60% and has not changed much since the 1970s. Modlin et al. (2008) reported that "…overall 5-year survival for pancreatic NETS varies from 97%..." to 30%, depending on the tumor subtype and degree of metastases (p. 62). Tsikitis et al. (2012) noted that the 5-year survival rate for patients with colon NETs has improved significantly since the 1970s—this may be due to an increase in colonoscopies. Öberg and Castellano (2011) observed that studies using the updated WHO classification for NETs have found that well-differentiated NETs have a better prognosis when compared to well- and poorly-differentiated neuroendocrine carcinomas. Lawrence, Gustafsson, Chan, et al. (2011) also indicated that poorly differentiated gastroenteropancreatic NETs are more aggressive and associated with a shorter survival time.

Neuroendocrine Tumors and Biomarkers

Researchers have not yet elucidated the molecular mechanisms of NETs, but it appears that the tumors are genetically distinct (Gilbert et al., 2010; Klöppel, 2007; Zhang et al., 2007). Modlin et al. (2008) stated, "The mechanisms that underlie

differentiation of cells of the diffuse endocrine-cell system are poorly understood" (p. 62). Like other types of cancers, there are biomarkers that contribute to the diagnosis of NETs, disease prognosis, monitoring, tumor pathology, clinical presentation, and treatment outcome of the disease (Ardill & Erikkson, 2003; Diebold et al., 2012; Modlin et al., 2008). Biomarkers can be measured in the patients' urine and/or blood plasma (Diebold et al., 2012). The use of radioimmunoassays for NET peptide hormones began in the mid-1960s and has expanded since then (Eriksson, Öberg, & Stridsberg, 2000). Finding a single, high-quality biomarker for NETs has been challenging because of their heterogeneous nature (Lawrence, Gustafsson, Kidd, et al., 2011). There are several biomarkers that are commonly used to differentiate between gastrointestinal NETs and pulmonary NETs in addition to those that act as general biomarkers of the disease. Many of the biomarkers that have been evaluated are related to secretory vesicles or located in the cytosol (Turaga & Kvols, 2011). Some examples are provided in the following paragraphs.

Neuron-specific enolase (NSE) is a cytosolic marker of the disease, but it is limited as a diagnostic biomarker because it has been found in non-NET tissues (Klöppel, 2007). Similarly, the neural cell adhesion molecule (NCAM), a cell membrane biomarker, is found in NET cells, but it is also detectable in some normal tissues (Klöppel, 2007; Turaga & Kvols, 2011). Synaptophysin, expressed separately from other NET biomarkers, is a small vesicle-associated marker (Klöppel, 2007; Turaga & Kvols, 2011). CgA is a universal biomarker for NETs and is discussed in-depth later in this chapter (Klöppel, 2007). CDX2, a transcription factor, is a reliable biomarker for midgut

NETs and shows promise for identifying pancreatic, rectal, and lung NETs (Klöppel, 2007). Other transcription factors have a role as well. Protein atonal homolog 1, neurogenin-3, and neuroD are involved in neuroendocrine cell differentiation, although the mechanisms that initiate differentiation are not well understood (Modlin et al., 2008; Turaga & Kvols, 2011). Another transcription factor, TTF-1, can be used as a marker for lung NETs (pulmonary carcinoid and poorly-differentiated neuroendocrine carcinoma subtypes; Klöppel, 2007). At least five somatostatin receptors have been identified as NET markers as well (Klöppel, 2007). These five receptors are generally overexpressed in gastroenteropancreatic NETs, specifically sst2 (Öberg & Castellano, 2011). As such, somatostatin analogues are beneficial therapeutic options for the management of functional gastroenteropancreatic NETs (Öberg & Castellano, 2011). Growth factors also seem to affect carcinoid progression (Zhang et al., 2007).

Despite the established knowledge about NET-related biomarkers, Öberg and Castellano (2011) identified "…an unmet need for more sensitive biomarkers for diagnosis and follow-up" (p. S3). There is a need to further characterize genes related to NETs for the development of molecular diagnostic screening tests (Öberg & Castellano, 2011). Ito et al. (2012) and Modlin et al. (2010) commented on the lack of biomarkers for the early diagnosis and management of NETs. Ito et al. (2012) also cited the need for biomarkers that can identify nonfunctional tumors. Research toward diagnostic markers and treatment targets is ongoing. Gilbert et al. (2010) pointed out that anti-cancer therapies, such as protein kinase inhibitors, can drive the search for NET biomarkers. The authors identified Hsp90, IGF1R, and EGFR as potential molecular targets for NETs,

indicating that further research was necessary because these could be anti-cancer targets for future NET treatments (Gilbert et al., 2010). Zhang et al. (2007) evaluated whether VEGF has a role in NET development and progression. Results from their in vivo study in xenograft mouse models indicated that VEGF expression was elevated in tumors and inhibited when treated with bevacizumab (Zhang et al., 2007). Moreover, they observed that VEGF expression was correlated with a transcription factor, Sp1, and there was an association between VEGF and metastases (Zhang et al., 2007).

The studies discussed in the previous paragraph illustrate the importance of understanding the effects of biomarkers on NETs. A broader knowledge base about biomarkers and their relationship with NETs could help clinicians optimize patients' disease management. This research focused on six novel biomarkers of the disease as they relate to QOL: CgA, gastrin, NKA, pancreastatin, serotonin, and 5-HIAA. These biomarkers and related studies are discussed in the sections that follow.

Chromogranin A. CgA is probably the most widely studied NET biomarker (Ardill & Erikkson, 2003; Eriksson et al., 2000; A. Vinik et al., 2009). The CgA protein is an acidic glycoprotein found in normal neuroendocrine cells and NET cells' neurosecretory vesicles—it is frequently detected in 60%-100% of NET patients' plasma (Kulke et al., 2011; Prestifilippo et al., 2012; Turaga & Kvols, 2011; Vinik & Gonzales, 2011). CgA is a precursor to peptides such as pancreastatin, and it fosters the creation of dense-core secretory granules in NET cells (Klöppel, 2007; Modlin et al., 2008; Prestifilippo et al., 2012). Plasma CgA is considered a useful marker for functional and nonfunctional pancreatic NETs (Ito et al., 2012; Metz & Jensen, 2008; Öberg et al.,

2012). Additionally, CgA is secreted in gastrointestinal NETs of the hindgut, midgut, and foregut as well as other tumor subtypes (Prestifilippo et al., 2012). Per Kulke et al. (2011), "elevated plasma CgA levels have been associated with poor overall prognosis in patients with NETs" (p. 940). It is a particularly useful biomarker for advanced disease and tumor recurrence as well (Seregni, Ferrari, Bajetta, Martinetti, & Bombardieri, 2001; Modlin et al., 2010). While Lawrence, Gustafsson, and Kidd, et al. (2011) commented that "the clinical utility of this tool is blunted…by the ubiquity of CgA in normal tissue," they also acknowledged that it is an important biomarker for diagnosing and managing gastroenteropancreatic NETs (p. 111).

CgA can be applied as a broad-spectrum diagnostic marker, used to assess treatment effectiveness, and act as a follow-up marker because it sensitive for NETs (Lawrence, Gustafsson, Kidd, et al., 2011; Öberg & Castellano, 2011; Prestifilippo et al., 2012; Turaga & Kvols, 2011). Toward the detection of NETs, CgA's sensitivity and specificity ranges from 70%-100% (Seregni et al., 2001; Vinik & Gonzales, 2011). Modlin et al. (2010) called it a "sensitive but nonspecific" NET biomarker (p. 2432). Studies have shown that it is more sensitive biomarker than either platelet serotonin or urinary 5-HIAA as well (Modlin et al., 2010).

Kulke et al. (2011) observed that plasma CgA measurements should be included in prospective clinical trials, even though it is not validated as a predictive biomarker. Despite its strengths, Ito et al. (2012) pointed out that there is conflicting literature about whether serum CgA is useful as a biomarker for tumor growth or management. CgA levels are affected in patients who regularly take proton pump inhibitors as well as in

patients with liver failure, renal failure, or chronic gastritis (Eriksson et al., 2000; Ito et al., 2012; Vinik & Gonzales, 2011).

Gastrin. Gastrin is another biomarker of the disease that contributes to the pathogenesis of gastric NETs (Burkitt, Varro, & Pritchard, 2009; Klöppel & Clemens, 1996). Gastrin is a peptide hormone that regulates the production and secretion of gastric acid as well as regulates the expression of gastric CgA via transcriptional mechanisms (Hocker, 2004). It is a diagnostic biomarker for gastric NETs and can be used to distinguish between subtypes of gastric carcinoids (Burkitt et al., 2009; Vinik & Gonzales, 2011). Furthermore, gastrin can be a biomarker for NETs in the bronchus, pancreas, stomach, and duodenum (Modlin et al., 2008). In a historic paper, Bostwick, Roth, Evans, Barchas, and Bensch (1984) found gastrin-releasing peptide in a sample of human lung neuroendocrine tumors. It is also a biomarker associated with NETs-related diarrhea and ZES (Burkitt et al., 2009; A. Vinik et al., 2009).

Neurokinin A. Recent studies have shown that NKA, a tachykinin, is a beneficial prognosis marker for patients with well-differentiated midgut NETs, the most common type of gastroenteropancreatic NETs (Ardill & Erikkson, 2003; Diebold et al., 2012; Dobson et al., 2013; Mamikunian et al., 2011). Modlin et al. (2008) previously stated that NKA can be a biomarker for NETs in the ileum at intermediate specificity. Turner et al.'s (2006) evaluation of 139 patients with midgut NETs confirmed that plasma NKA is an independent prognostic marker, making it one of the first studies to identify NKA's ability to predict survival. NKA can be applied as a marker for individuals with poor prognosis and used to identify patients who need changes in their treatment to improve

survival (Diebold et al., 2012; Mamikunian et al., 2011). NKA is also one of the biomarkers for flushing related to NETs and possibly carcinoid heart disease (A. Vinik et al., 2009; Dobson et al., 2013).

A comparison of two NKA assays using plasma samples from patients in the United Kingdom and United States showed promising results for the biomarker (Diebold et al., 2012; Mamikunian et al., 2011). Mamikunian et al. (2011) performed the cross-validation of these two methodologically different, validated assays. Results from the regression analysis of the NKA values indicated a statistically significant high degree of correlation between the two populations (Mamikunian et al., 2011). This cross-validation indicated that the reliability of these assays' ability is able to predict clinical outcomes as well as a level of equivalence, which is beneficial for future collaborative studies (Mamikunian et al., 2011).

Research also demonstrated that lower "…circulating plasma levels of NKA are associated strongly with enhanced survival" (Diebold et al., 2012, p. 1173). Patients with a NKA level less than 50 pg/mL had a much higher 3-year survival rate (65%) than those with NKA levels greater than 50 pg/mL (10%; Diebold et al., 2012; Mamikunian et al., 2011). Of note, patients that had NKA levels that were reduced by treatment returned to a survival rate similar to NKA patients that never had a higher level of the marker (Diebold et al., 2012; Mamikunian et al., 2011).

Based on the above information, Diebold et al. (2012) compared short-term survival of patients with midgut NETs who had consistently higher (> 50 pg/mL) and lower (< 50 pg/mL) NKA levels. They found that the serial measurement of NKA in

patients with well-differentiated midgut NETs was able to identify patients with "…a poor short-term prognosis if left untreated" (Diebold et al., 2012, p. 1175). Furthermore, they also found that patients with higher NKA levels that dropped after treatment had improved survival (Diebold et al., 2012). The investigators concluded that NKA is a sensitive biomarker for monitoring therapy effectiveness (Diebold et al., 2012).

Pancreastatin. Pancreastatin is a post-translational peptide product generated from CgA and present in NETs (Ito et al., 2012; Vinik & Gonzales, 2011). Unlike CgA, it is not affected by patients taking proton pump inhibitors (Ito et al., 2012). It has been shown "…to be a sensitive indicator of progressive disease" in midgut NETs more recently (Diebold et al., 2012, p. 1172). High levels of plasma pancreastatin (greater than 500 pmol/L) are associated with poor outcome/survival in NET patients (A. Vinik et al., 2009; Vinik & Gonzales, 2011). Pancreastatin is achieving acceptance as a midgut NET biomarker for diagnosis and monitoring treatment response (Mamikunian et al., 2011; Vinik & Gonzales, 2011). Pancreastatin also correlates with liver metastases (A. Vinik et al., 2009). In a study of NET patients who had hepatic artery chemoembolization, extremely elevated plasma pancreastatin levels (greater than 5000 pg/mL) were connected to higher rates of periprocedural mortality (A. Vinik et al., 2009; Vinik et al., 2011). As a novel biomarker of NETs, further studies on pancreastatin are warranted.

Serotonin. Serotonin can be a marker for NETs in the bronchus and ileum with intermediate specificity (Modlin et al., 2008). Foregut NETs produce more serotonin than midgut NETs (A. Vinik et al., 2009). Less commonly, serotonin has been measured in serum to monitor the functionality and growth of well-differentiated midgut NETs

(Diebold et al., 2012). Of note, patients with pancreatic NETs generally do not secrete serotonin, but a small percentage of these tumors do (Kawamoto et al., 2011l Kulke et al., 2011). In a small review of clinical cases, Kawamoto et al. (2011) discussed serotonin-producing pancreatic NETs causing pancreatic duct obstruction and fibrosis. Serotonin is also one of the biomarkers for flushing associated with foregut and midgut tumors (A. Vinik et al., 2009; Vinik & Gonzales, 2011). In animal and human studies, serotonin was associated with carcinoid heart disease—it may have a role in its pathogenesis (Dobson et al., 2013; A. Vinik et al., 2009). More studies related to serotonin as a marker are necessary to clarify its role in NETs.

5-hydroxyindoleacetic acid. Urinary 5-HIAA is a longstanding biomarker for NETs (Eriksson et al., 2000). It can be measured as a surrogate marker for serotonin because it is a breakdown product of the latter, and it has a reported specificity of 88% (Modlin et al., 2008; Vinik & Gonzales, 2011). An historic study with a larger patient population ($N = 290$) reported 5-HIAA's specificity and sensitivity at 100% and 35%, respectively (Seregni et al., 2001). Kulke et al. (2011) and Diebold et al. (2012) noted that urinary 5-HIAA is a useful diagnostic marker for patients who have metastatic carcinoid tumors in the midgut. In their study, Van der Horst-Schrivers et al. (2007) determined that urinary 5-HIAA functions as an independent prognostic marker that can be used during patients' initial and follow-up visits. It can be used to assess tumor progression and functionality in midgut NETs as well (Diebold et al., 2012). Of note, 5-HIAA is also a biomarker for NETs in the bronchus and ileum at intermediate and high specificity, respectively (Modlin et al., 2008). 5-HIAA is also one of the biomarkers for

NET-related flushing and has been linked to carcinoid heart disease progression (Dobson et al., 2013; A. Vinik et al., 2009). High urinary levels of 5-HIAA are associated with lower survival rates as well (Van der Horst-Schrivers et al., 2007).

Despite its usefulness as a NETs marker, 5-HIAA can have problematic false positives, and certain medications or foods can increase urinary 5-HIAA levels (Mamikunian et al., 2011; Vinik & Gonzales, 2011). Due to the issues related to false positives, it is recommended that 5-HIAA is measured via a 24-hour urine collection (Tellez, Mamikunian, O'Dorisio, Vinik, & Woltering, 2013). Tellez et al. (2013) compared 5-HIAA values from a 24-hour urinary collection with plasma 5-HIAA values in a group of 115 patients. The resulting correlations from the regression analysis were statistically significant, indicating that plasma and urinary 5-HIAA levels from the same patient are similar (Tellez et al., 2013). Plasma 5-HIAA measures could be a viable alternative to urinary 5-HIAA measures (Tellez et al., 2013). In another study, Dobson et al. (2013) found that plasma 5-HIAA had significant discriminatory value for carcinoid heart disease diagnosis in a population of 187 NET patients. Additional research about the relationship between 5-HIAA and NETs is still needed.

Neuroendocrine Tumors and Quality of Life

Arthur Pigou defined QOL in 1920—the WHO revisited the concept and incorporated health in its definition in 1948 (CDC, 2011; Ormel et al., 1997; Vinik et al., 2011; Vinik et al., 2014). QOL is a complex, multidimensional concept comprised of patients' experiences, their well-being, and how their illness affects their lives (CDC, 2011; E. Vinik et al., 2009). It is an indicator for health outcomes, responds to clinical

changes, and can be used to predict morbidity/mortality as well (CDC, 2011; Ormel et al., 1997; Vinik et al., 2011; Vinik et al., 2014).

In their explanatory model, Ormel et al. (1997) illustrated how a disease (or disorder) results in physical and mental impairments, leading to symptoms and functional limitations—these things ultimately impact an individual's QOL. As noted in other studies, QOL is the dependent variable that changes based on the domains (independent variables) in the tool (e.g., physical functioning, positive/negative attitude, and so forth; Stuifbergen et al., 2000). The individual domains in an instrument can measure the physical, social, and emotional aspects that contribute to overall health-related QOL. Tools that measure QOL "…make it possible to demonstrate scientifically the impact of health on quality of life, going well beyond the old paradigm that was limited to what can be seen under a microscope" (CDC, 2011, para. 6).

Over the last decade, a greater interest has arisen in patient-reported QOL, and it has become an endpoint for clinical trials (E. Vinik et al., 2009; Vinik et al., 2011). Since the 1970s, instruments to measure health-related QOL have transitioned from generic to disease-specific (Vinik et al., 2011; Vinik et al., 2014). The United States Food and Drug Administration requires that clinical trials for new therapies measure QOL/patient-reported outcomes because this information can help researchers determine whether the disease or intervention is affecting the participants (Vinik et al., 2011; Vinik et al., 2014). QOL can help physicians better understand the effects of a chronic illness (such as NETs) on a patient as well as the relationship between risk factors (e.g., behaviors) and a disease (CDC, 2011; Ormel et al., 1997; E. Vinik et al., 2009; Vinik et al., 2011). Davis (2009)

pointed out that QOL is one of the most critical measurable outcomes for cancer patients. It is possible that some treatments may improve QOL, while others (like chemotherapy or radiation) can adversely affect it (Davis, 2009; Vinik et al., 2011; Vinik et al., 2014). Historically, Larsson, von Essen, and Sjödén's (1998) QOL study in patients with gastrointestinal NETs showed a need for enhanced communication between hospital staff and patients. Researchers indicated that NET patients have diminished QOL when compared to a general population as well (Fröjd et al., 2007; Haugland et al., 2013; Larsson et al., 2001; E. Vinik et al., 2009; Vinik et al., 2011; Vinik et al., 2014; Yadegarfar et al., 2013). Consequently, there is not a vast body of literature regarding QOL and NETs (Yadegarfar et al., 2013). This remains an understudied area in the field, which provides this study the opportunity to make a contribution to existing knowledge about QOL and NETs.

NET-Specific QOL Instruments

In 2004, one of the first health-related QOL tools for NETs was developed and later validated, the Norfolk QOL-NET (E. Vinik et al., 2009; Vinik et al., 2014). The Norfolk QOL-NET is a 72-item instrument that "…captures 11 symptoms and it measures both frequency and severity of symptoms" (Vinik et al., 2011, p. 100). The Norfolk QOL-NET has seven domains, including physical functioning, respiratory, depression, cardiovascular, gastrointestinal, flushing, and positive/negative attitude (E. Vinik et al., 2009). Of these domains, physical functioning contributes the most (40% or 26/65 items) to overall QOL score (E. Vinik et al., 2009). The Norfolk QOL-NET is described in greater detail in Chapter 3.

The EORTC QLQ-C30 QLQ-GINET-21 is another clinically sensitive, validated NET-specific QOL tool (Yadegarfar et al., 2013). The EORTC QLQ-C30 by itself is a validated, 30-item questionnaire that measures "generic aspects of cancer" (Davies et al., 2006; Vinik et al., 2011, p. 99; Yadegarfar et al., 2013). Responses are given based on a 4-point Likert scale (Yadegarfar et al., 2013). In an effort to capture disease specific information, modules are attached to the QLQ-C30. The QLQ-C30 QLQ-GINET-21 includes a 21-question, NET-specific module (with three multi-symptom scales) with the standard QLQ-C30 tool that was developed by the EORTC QOL group (Davies et al., 2006; Yadegarfar et al., 2013). This is in contrast to the Norfolk QOL-NET, "…an all-inclusive single tool for measuring the subjective, self-reported effects of NETs on QOL" (E. Vinik et al., 2009, p. e94). The QLQ-GINET21 itself is responsive for the measurement of NETs in the gut, liver, and pancreas (Yadegarfar et al., 2013). The Norfolk QOL-NET measures symptom severity and frequency for eleven symptoms over a 4-week period (E. Vinik et al., 2009; Vinik et al., 2011). The eleven symptoms include the following: flushing; joint/bone pain; other pain; peripheral edema; wheezing; diarrhea or constipation; rash; cyanosis; telangiectasia; fatigue; and coughing (E. Vinik et al., 2009). In comparison, the EORTC QLQ-C30 QLQ-GINET-21 asks about a single-week timeframe (except for the question about sexual activity), and they do not inquire about the same systems (E. Vinik et al., 2009; Vinik et al., 2011).

NETs and QOL Studies

As mentioned previously, there is not a vast body of literature about QOL and NETs. Some studies used generic tools to capture QOL in NET patients, while others

used the European or Norfolk QOL-NET instruments. These studies are discussed in the following section.

Fröjd et al. (2007) used the EORTC QLQ-C30 to evaluate QOL and psychosocial function in a Swedish population of NET patients. Participants' levels of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS; Fröjd et al., 2007). Fröjd et al. (2007) created an instrument with a 4-week timescale for three major dimensions of aspects of distress: social restrictions (5 aspects); emotional (9 aspects); and physical (10 aspects). Each aspect was scored via a 5-point Likert scale (Fröjd et al., 2007). To create this instrument, the investigators used data from semi-structured interview questions given to patients and nurses in a previous study (Fröjd et al., 2007). Patient data from the three instruments were compared with data from the Swedish general population (Fröjd et al., 2007). An ANOVA and one-sample t-tests were used to analyze data. Interestingly, the investigators discovered that QOL and psychosocial function were stable during patients' first year post-diagnosis (no significant differences); however, after that time period, NET patients' QOL (particularly emotional distress) was lower than that of the general population (Fröjd et al., 2007). At all assessments, patients had higher levels of cognitive, emotional, physical, and social function than overall QOL and role function ($p<0.01$; Fröjd et al., 2007). Compared against the general population, patients had increased issues with diarrhea and fatigue as well as lower overall QOL and role function scores (Fröjd et al., 2007). Patients had increased worries about caring for their family, their family's situation, and medical check-ups at all assessment points too (Fröjd et al., 2007). Physicians and researchers

could use these results to implement methods or interventions that would reduce the distress/worry for their NET patients.

In a cross-sectional study, Haugland, Vatn, Veenstra, Wahl, and Natvig (2009) compared QOL data for 196 NET patients and 5,258 members of the general Norwegian population. QOL was measured with the standard SF-36 instrument. ANOVA and t-tests were used to analyze the QOL data (Haugland et al., 2009). As anticipated, NET patients had significantly lower QOL scores than the general population (Haugland et al., 2009). In particular, the vitality, general health, and physical limitation scales had the lowest scores (Haugland et al., 2009). Investigators found that elderly individuals (older than 70 years of age) had lower physical functioning and physical limitation scores, which conflicted with previous studies that did not have a significant difference between QOL and age (Haugland et al., 2009). Individuals who were retired also had lower scores in these categories than individuals who were working (Haugland et al., 2009). Education appeared to be a factor as well—participants with higher education levels had better physical functioning scores than participants with less education (Haugland et al., 2009).

Haugland et al. (2013) looked for changes in QOL, stress, and self-efficacy in 37 NET patients who participated in a multidisciplinary educational intervention based on self-efficacy principles. The intervention provided patients with problem-solving strategies to manage and live with NETs. The investigators used the well-established, generic SF-36 tool for QOL, a modified version of the Impact of Event Scale for stress, and the General Self-Efficacy Scale for self-efficacy (Haugland et al., 2013). After the intervention, participants showed significant improvements in stress, self-efficacy, and

the physical component of QOL (Haugland et al., 2013). Men had a significantly increased change in the physical component of QOL when compared to female participants as well (Haugland et al., 2013).

Knox et al. (2004) assessed survival and longitudinal functional QOL in patients who had undergone resection for hepatic carcinoid metastasis (HCM). Patients with HCM have a poor prognosis (5-year survival rate of 20%-30%) and carcinoid syndrome (Knox et al., 2004). The investigators measured functional QOL (via Karnofsky functional scores), three biomarkers (CgA, NSE, and 5-HIAA), and survival as their main outcome measures (Knox et al., 2004). Knox et al. (2004) observed a significant improvement in functional QOL after the surgical resection in addition to tumor marker normalization and prolonged survival. Of note, there was a significant association between resection of greater than or equal to 90% tumor volume and normalization of the tumor markers as well as survival (Knox et al., 2004).

There have been some studies that compared QOL to NET biomarkers (Korse et al., 2009; Larsson et al., 2001; Vinik et al., 2011; Vinik et al., 2014). Over a decade ago, Larsson et al. (2001) used the EORTC QLQ-C30 and HADS to evaluate QOL and anxiety/depression, respectively, in patients with midgut NETs during their first year of treatment. Patients' functional ability was measured via the Karnofsky Performance Status Scale (Larsson et al., 2001). Patient data were compared against data from the general Swedish population as well (Larsson et al., 2001). These three instruments were administered at baseline and an additional four times across a 12-month period (Larsson et al., 2001). Investigators also obtained participants' plasma CgA and urinary 5-HIAA at

each time point as well (Larsson et al., 2001). One-sample t-tests were used to analyze the data from the instruments, and Pearson's correlations were done between the instrument scores and biomarkers. Larsson et al. (2001) did not find a relationship between the biomarkers and QOL; furthermore, tumor marker levels did not correlate with psychosocial function. However, there were significant correlations between CgA and 5-HIAA with diarrhea at the 12-month point (Larsson et al., 2001). They did observe significant improvement in symptoms in patients, including anxiety, flushing, and nausea/vomiting (Larsson et al., 2001). Patients had increased muscle pain and decreased physical functioning over the year as well (Larsson et al., 2001). When compared to the general population, patients had lower overall QOL too (Larsson et al., 2001). Interestingly, the authors of this study cited a need for a NET-specific assessment tool in their conclusion (Larsson et al., 2001).

Korse et al. (2009) compared urinary 5-HIAA and CgA "…as part of the evaluation of the response to treatment with a somatostatin analog" in a European patient population (p. 297). Response to treatment was evaluated using the EORTC QLQ-C30 with the carcinoid-specific symptom scale, QLQ-GINET21 (Korse et al., 2009). Korse et al. (2009) specifically focused on diarrhea, physical functioning, and overall QOL. Mixed linear models were used to evaluate the QOL and tumor marker outcomes, while Cox regression analysis was used to assess survival (Korse et al., 2009). CgA correlated significantly with overall QOL and physical functioning, whereas 5-HIAA did not correlate with either of them (Korse et al., 2009). There was also a significant association between survival time and CgA levels, but not between survival time and 5-HIAA (Korse

et al., 2009). Korse et al. (2009) stated that their findings implied that CgA is a better biomarker for NET patients than 5-HIAA.

Vinik et al. (2011) conducted a study where 29 patients filled out both the Norfolk QOL-NET and the EORTC QLQ-C30 QLQ-GINET-21. Results from the questionnaires were also compared against biomarkers (Vinik et al., 2011). Spearman's nonparametric correlations were used to obtain correlation data between the questionnaires and biomarkers; additionally, regression analysis was employed to discern whether or not results from the two questionnaires correlated with each other (Vinik et al., 2011). With the exception of the cardiovascular domain, the QOL scores from the two questionnaires correlated positively; notably, the EORTC QLQ-C30 QLQ-GINET-21 does not have cardiovascular-related questions (Vinik et al., 2011). The Norfolk QOL-NET's physical functioning domain had the strongest correlation with the total score of both questionnaires (Vinik et al., 2011). Correlation between the two questionnaires indicated that they are both effective in the clinic (Vinik et al., 2011). Serotonin had a significant, positive correlation with total QOL from both questionnaires as well (Vinik et al., 2011). Additional research related to this study found correlations between tumor burden and three of the Norfolk QOL-NET's domains: physical functioning, depression, and gastrointestinal (Vinik et al., 2014). A significant correlation between the biomarker serotonin, total QOL from the Norfolk QOL-NET, total QOL from the EORTC QLQ-C30 QLQ-GINET-21, and the three domains (physical functioning, depression, and gastrointestinal) was observed as well (Vinik et al., 2014). It was noted that the Norfolk

QOL-NET has more questions in their respiratory and flushing domains than the EORTC QLQ-C30 QLQ-GINET-21 as well (Vinik et al., 2014).

Summary

NETs, originating from neuroendocrine cells, are a rare, complicated collection of neoplasms that are difficult to diagnose. Clinical pathogenesis and presentation are influenced by the amines and hormones produced by these tumors, which is why it is critical to continue researching how these biomarkers and primary tumor sites affect NETs. While there is a more known about some biomarkers of the disease (such as CgA, serotonin, and 5-HIAA) than others, the literature demonstrated that additional studies are warranted. There is less information available about gastrin, NKA, and pancreastatin's roles in NETs, which indicates a need for more studies about these novel biomarkers.

As a challenging chronic illness, NETs also affect patients' QOL. In particular, NETs can lessen patients' physical functioning and total QOL. Although there is a greater interest in patient-reported outcomes and NET research, there is not a vast body of literature related to QOL and NETs. There is a need for further studies that provide a deeper understanding of the relationship between NETs and QOL. Given what is known about the impact made by disease biomarkers and NETs with different origin sites on the various aspects of the disease, it is feasible to hypothesize that the tumor of origin and/or biomarkers expressed by those tumors could affect NET patients' QOL. The present study moved beyond previous studies to determine whether there was a relationship between the total QOL of patients with different primary tumor sites. The relationship

between total QOL and disease-specific biomarkers was also assessed. The methodology used to address this gap in knowledge is explained further in Chapter 3.

Chapter 3: Research Method

Introduction

The purpose of this study was to examine the relationship between total QOL and patients' primary tumor sites in addition to investigating the relationship between total QOL and six novel biomarkers of NETs. This chapter discusses the study's design and approach. It also includes a description of the secondary database from the Neuroendocrine Unit at Eastern Virginia Medical School in Norfolk, Virginia, henceforth referred to as the *QOL-NET database*. The Norfolk QOL-NET instrument is described along with the study's analytical approach and ethical considerations as well.

Research Design and Rationale

I took a quantitative approach to analyzing the secondary, de-identified clinical data that were collected using the Norfolk QOL-NET instrument to evaluate the relationships between these variables. Furthermore, the data were quantitative, cross-sectional, and only generalizable to the NET patient population in the same age range as the patients in the dataset. A quantitative approach aligned with the analysis of questionnaire-based numerical data and the study's purpose to advance knowledge in the discipline. The total QOL score was the dependent variable. The biomarkers and primary tumor sites were evaluated as independent variables to determine whether they affected patients' total QOL. There were no time or resource constraints associated with this research.

Methodology

Population

For this study, I used data from 134 female and male patients diagnosed with NETs. The age range for these patients was 18-85 years of age.

Recruitment, Participation, and Data Collection

Data in the QOL-NET database were collected from patients with a diagnosed NET who were asked to participate in a study during clinic visits (Vinik et al., 2011; A. Vinik & E. Vinik, personal communication, July 1, 2015). Patients signed informed consent forms to participate and have their de-identified data used in research (Vinik et al., 2011; A. Vinik & E. Vinik, personal communication, July 1, 2015). Patients who did not have a NET were not asked to participate. I did not have any information about how the patients in the clinic were different from other patients, nor did I have information about whether they were referred there, which may be considered a limitation. It was also unknown how the patients who agreed to participate were different from those who did not.

The QOL-NET database was in an Excel file that contained information for 134 NET patients. Dr. Aaron Vinik (Professor, Eastern Virginia Medical School Neuroendocrine Unit) provided the QOL-NET database and gave permission for it to be used in this study (Appendix A). All of the data were already de-identified, and patients were listed by a numerical Patient ID in the database.

Sample and Sampling Procedures

The patient sample for the QOL-NET database was obtained in the clinic, as patients with a NET were asked to take part in the survey (Vinik et al., 2011; A. Vinik & E. Vinik, personal communication, July 1, 2015). There were data available from 134 individuals in this single database. For this study, sample size was determined using the online calculator from Raosoft (Raosoft Inc., 2004). This online calculator takes margin of error, confidence level, population size, and response distribution into account when determining a minimum recommended sample size (Raosoft Inc., 2004). A standard margin of error (5%) was selected along with a standard confidence level of 95% (α = .05). The population size was given as 134, the number of individuals in the database. The response distribution was entered as 50%. Per Raosoft, Inc. (2004), when the response distribution to questions is unknown, using 50% is appropriate because it will yield a larger sample size. For this study, the recommended sample size from the Raosoft calculator was 100 individuals. Consequently, data from all 134 patients were analyzed because they were available, and using all of the data in the single dataset avoided having to make any type of limiting selection that could have introduced sampling bias into the study.

Instrumentation and Operationalization of Constructs

The Norfolk QOL-NET is a 72-item, disease-specific instrument designed in 2004 to fill a gap in neuroendocrine tumor and carcinoid research literature (E. Vinik. et al., 2009; Vinik et al., 2014). The development and validation of the Norfolk QOL-NET took investigators three years to complete at Eastern Virginia Medical School in Norfolk,

Virginia (E. Vinik et al., 2009). Questions were initially developed with a panel of experts to ensure content validity, and the tool was later pilot tested with NET patients in a focus group (E. Vinik et al., 2009). The experts and patients provided useful suggestions that facilitated the refinement of the instrument (E. Vinik et al., 2009).

The instrument includes a cover page that asks patients about their history with NETs, common NET symptoms, and demographic information. The Norfolk QOL-NET is scored on a 5-point Likert scale (E. Vinik et al., 2009). It was designed to capture symptom severity and frequency along with activities of daily living, somatostatin injections, and a feelings scale (E. Vinik et al., 2009). A copy of the tool is presented in Appendix B. The instructions in the first three sections of the tool ask the patients to rate these items over the last 4 weeks. The instructions for the final part of the tool, the feelings scale, asks patients to describe how often they felt or behaved a certain way over the last seven days (E. Vinik et al., 2009). Items 1-11 (Part 1a) measure the frequency of NETs-related symptoms and is scored on a range of "no symptoms" to "more than once a day" (E. Vinik et al., 2009). Items 12-22 (Part 1b) measure the severity of NETs-related symptoms, ranging from "no symptoms" to "extremely severe" (E. Vinik. et al., 2009). The remaining items in the questionnaire are as follows: items 23-54 (Part 2) measure activities of daily living; items 55-58 (Part 3) measure how patients feel about their somatostatin/sandostatin injection; and items 59-72 (Part 4) comprise the "Feelings Scale" (E. Vinik et al., 2009).

Psychometric factor analysis was performed on the instrument's items to ascertain the number of domains within it (E. Vinik et al., 2009). Ultimately, the psychometric

analysis identified seven domains in the Norfolk QOL-NET: cardiovascular, depression, flushing, gastrointestinal, physical functioning, positive/negative attitude (referred to as "attitude" henceforth), and respiratory (E. Vinik et al., 2009; Vinik et al., 2014).

A Cronbach's α test was used to assess internal consistency of the items in the questionnaire, and discriminatory capability was assessed via a case-control study performed at the Neuroendocrine Unit (E. Vinik et al., 2009). Results from the Cronbach's α for each domain was 0.86 or higher, indicating a high level of internal consistency within each of the scales (E. Vinik et al., 2009). The results from the case-control study showed that the total QOL score was capable of discriminating between a NET population and a healthy population, but the scores for the specific domains were not significant discriminators, indicating that the NET patients have symptoms that are common in healthy individuals (E. Vinik et al., 2009, p. e93). This finding highlights part of the challenge of diagnosing NET patients—healthy individuals may also experience fatigue, abdominal pain, coughing, irritable bowel syndrome, and other similar symptoms that are common for NET patients (E. Vinik et al., 2009). The case-control study also showed that physical functioning, depression, flushing, and gastrointestinal domains were all significantly higher for NET patients, whereas the cardiovascular, respiratory, and attitude domains were not significant (E. Vinik et al., 2009). Investigators evaluated the instrument's reliability in the same cohort of patients via a test-retest analysis, and the results showed that there were no significant differences between the first questionnaire and the second questionnaire, demonstrating good reliability. (E. Vinik et al., 2009).

Operationalization

The database contained the following data: basic demographic data on age, gender, and race; patients' yes/no responses to the Norfolk QOL-NET cover page (Appendix B); their numerical responses to the 72-item questionnaire; total QOL scores for all patients; numerical values for pancreastatin, NKA, serotonin, 5-HIAA, CgA, and gastrin; whether the biomarker values are normal (nominal data: yes, no, no-low); and the primary tumor site (nominal data). For all patients, age was a numerical value. Gender and race were both categorical variables. The following questions from the cover page of the Norfolk QOL-NET had dichotomous responses (yes or no): have you been told you have or had a carcinoid tumor; do you have a family history of neuroendocrine tumors; do you have an endocrine tumor; do you have an endocrine tumor; in the past month, have you lost weight without trying; do you have a history of high blood pressure; do you have any carcinoid syndromes; do you have flushing; is the flushing hot; and do you sweat when you flush.

Questions 1-72 of the Norfolk QOL-NET are scored numerically. All of the questions and scales are in the copy of the instrument located in Appendix B. Questions 1-11 (Part Ia: Symptom Frequency), Questions 12-22 (Part Ib: Symptom Severity), Questions 23-53 (Part II: Activities of Daily Life), and Questions 59-72 (Part IV: Feelings Scale) of the Norfolk QOL-NET are scored on a 5-point Likert scale. Question 54 (Part II) is scored on a 6-point Likert scale. Questions 55-58 (Part III: Somatostatin Injection Scale") are not part of the total QOL score, but they are scored on a 5-point Likert scale.

Numerical data for total QOL and the total scores for the seven domains (depression, flushing, respiratory, gastrointestinal, cardiovascular, physical functioning, and attitude) were in the database as well. The biomarker data for pancreastatin, NKA, serotonin, 5-HIAA, CGA, and gastrin were also in the database. These were continuous, interval data. Additionally, the database contained dichotomous variables (yes/no) called *Pancreastatin Normal*, *NKA Normal*, *Serotonin Normal*, *CGA Normal*, and *Gastrin Normal*.

Data Analysis Plan

Descriptive statistical analyses were conducted on the following patient data from the dataset: data from the first page of the QOL-NET about patients' history with NETs, common NET symptoms, and demographic information; all 72 questions in the QOL-NET; total QOL score; scores for the seven domains; and biomarker data. The data from NET patients were analyzed using SPSS version 23 to answer two research questions:

Research Question 1: What is the relationship between the primary tumor site and NET patients' total QOL score?

$H_0$1: There is no relationship between the primary tumor site and NET patients' total QOL score.

$H_1$1: There is a relationship between the primary tumor site and NET patients' total QOL score.

Research Question 2: How does the presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affect the total QOL score for NET patients?

$H_0$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) does not affect the total QOL score for NET patients.

$H_1$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affects the total QOL score for NET patients.

For Research Question 1, primary tumor site was treated as the independent variable, and total QOL score was the dependent variable. It was hypothesized that there was a relationship between the primary tumor site and total QOL. With a categorical independent variable and a continuous dependent variable, a one-way ANOVA test was used to assess the relationship between primary tumor site and total QOL score. A one-way ANOVA looked for differences among the means of the primary tumor sites, and it was followed by a post hoc test (e.g., a Tukey HSD test) to determine where the differences were in this patient population. Any results with a p-value less than 0.05 were considered significant and supportive of the hypothesis that there was a relationship between the primary tumor site and total QOL score.

Related, separate one-way ANOVAs were also used to determine whether there was a relationship between the following: total QOL (dependent variable) and age groups (independent variable; 18-29 years; 30-39 years; 40-49 years; 50-59 years; 60-69 years; and 70-85 years); total QOL and gender (independent variable; male and female); and total QOL and race (independent variable). A post hoc test was also conducted for these analyses. A multiple linear regression analysis was conducted to determine whether multiple independent variables (age, gender, race, and primary tumor site) affected total QOL.

For Research Question 2, the presence of NET biomarkers (categorical variable) was treated as the independent variable, and total QOL score (continuous variable) was the dependent variable. It was hypothesized that specific NET biomarkers affected the total QOL score for NET patients. A one-way ANOVA was also used in this analysis, followed by a post hoc test. Any results with a p-value less than 0.05 was considered significant and supportive of the hypothesis that there was a relationship between the NET biomarkers and total QOL score. A multiple linear regression analysis was also conducted to determine whether multiple independent variables (age, gender, race, and biomarker presence) affected total QOL.

Threats to Validity

Self-reported data can be limiting and introduce potential bias to a study, which threatens internal validity. Studies that use self-reported data can be affected by recall bias, as patients may not clearly remember the information asked by the survey questions. Reporting bias could also threaten the study's internal validity because patients may have not answered questions accurately for whatever reason. Selection bias was another potential threat to validity because the patients in the QOL-NET database were selected based on having a NET.

One of this study's assumptions was that patients responded to the Norfolk QOL-NET honestly. It was assumed that the biomarker measures were clinically valid as well. The fact that researchers previously validated the Norfolk QOL-NET and established its reliability reduced some threats to the study's internal validity (E. Vinik et al., 2009). It was assumed that what was measured by the instrument is representative of NET

patients' QOL. Data were not generalized to any population other than a NET patient population in the same age range to reduce any threat to external validity. The differences in the interpretation between age groups may be a limitation and are discussed further in Chapter 5. An erroneous conclusion about the associations between variables in the study could have threatened statistical conclusion validity. A reliable instrument and an adequately powered study reduced this type of threat to validity.

Ethical Procedures

Prior to initiating the study, Institutional Review Board (IRB) approval was obtained from the Walden University IRB (IRB approval number: 03-29-16-0245646). Since archival data were being used, there were no ethical concerns related to recruitment or data collection. Dr. Vinik of Eastern Virginia Medical School granted permission to use the QOL-NET database for the purpose of this study (Appendix A). Data in the QOL-NET database were already de-identified; thus, there was no information that could have been used to identify any of the patients who filled out the Norfolk QOL-NET instrument. The de-identified data came from patients who provided consent. The database is stored on my personal computer, and I am the only one with access to it. It will remain confidential and be password-protected to ensure that it is secure. The QOL-NET database will be maintained securely for five years, at which point it will be destroyed.

Summary

Secondary QOL, primary tumor site, and biomarker data from 134 NET patients were evaluated to answer two research questions. The first question assessed the

relationship between primary tumor site and total QOL score. The second question examined whether specific NET biomarkers affected total QOL score. The results from these analyses and whether they answered the two research questions are discussed in Chapter 4.

Chapter 4: Results

Introduction

The purpose of this quantitative study was to examine the relationship between total QOL and patients' primary tumor sites in addition to investigating the relationship between total QOL and six novel biomarkers of NETs (5-HIAA, CgA, gastrin, NKA, pancreastatin, and serotonin). The research questions and hypotheses for this study are as follows:

Research Question 1: What is the relationship between the primary tumor site and NET patients' total QOL score?

$H_0$1: There is no relationship between the primary tumor site and NET patients' total QOL score.

$H_1$1: There is a relationship between the primary tumor site and NET patients' total QOL score.

Research Question 2: How does the presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affect the total QOL score for NET patients?

$H_0$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) does not affect the total QOL score for NET patients.

$H_1$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affects the total QOL score for NET patients.

The secondary dataset and the results from the data analyses of the NET patients' data in the QOL-NET dataset are discussed in this chapter. The findings from those analyses are also summarized.

Data Collection

Secondary, de-identified clinical data (collected in 2011-2012 using the Norfolk QOL-NET instrument) were evaluated in this study. The dataset contained QOL, primary tumor site, and biomarker data for 134 female and male patients diagnosed with NETs. Prior to starting the analyses, the Excel dataset was searched for any anomalies and missing data. Throughout the dataset, missing data were assigned a missing data code, 99. For the analyses, 99 was entered as a discrete missing value for each variable in SPSS version 23. In the demographics data, there were also instances where "N/A" was entered into a field. These instances were also assigned a second missing data code, 98. (For the demographic variables, both 98 and 99 were entered as discrete missing values in SPSS.)

Under the *Primary Tumor Site* variable, an undefined acronym was found, "TI." Per a personal communication with Dr. Vinik, the owner of the QOL-NET database, "TI" represents small intestine carcinoids associated with appendix tumors, and it is appropriate to refer to them as "appendix/small bowel" in the dataset (A. Vinik & E. Vinik, personal communication, May 13, 2016). As such, all instances of "TI" were changed to "appendix/small bowel" under this variable. Further examination of the *Primary Tumor Site* variable showed that some patients had an unknown primary tumor site, which is not unexpected with NETs (Keiser, Bergsland, & Nakakura, 2012). There were four other patients who had a primary tumor site unlike the rest of the patients

(kidney, cecum, TI + pancreas, and pheochromocytoma). Since having a single data point in each of these additional primary tumor site categories would complicate the analyses, they were grouped together as "Other." Only one patient had jejunum listed as the primary tumor site. Since the jejunum is part of the small intestine, that patient was included in the "Small Bowel" group. Given the large number of primary tumor sites, there was concern that they would affect the reliability of the analyses for Research Question 1. As such, the primary tumor sites were condensed into their larger organ groups when possible. A variable was created for this purpose called *Primary Tumor Site Condensed*. Colon, rectal, and appendix were combined into a "Large Bowel" group. Cecum was moved out of "Other" to the "Large Bowel" group as well. Duodenum and ileum were added to the "Small Bowel" group.

There were also other variables created for analyses purposes. For the one-way ANOVA and regression analyses, an *Age Groups* variable was created that assigned patients to one of six groups based on their age: 18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, and 70-85 years. All of the biomarkers except 5-HIAA had categorical variables (yes/no), *[Biomarker Name] Normal*. As such, a *5-HIAA Normal* variable was created based on the normal range provided by Dr. Vinik (A. Vinik, personal communication, May 13, 2016). Since there was little diversity in the *Race* variable, a new variable (*Race2*) was created where the "W/NA" (White/Native American) and "H" (Hispanic) categories were grouped together under "Other," giving the variable three levels: "White," "Black," and "Other." Based on the information from the six *[Biomarker] Normal* variables, I created a variable called *Presence of Abnormal*

Biomarkers to account for patients having none, one, or multiple abnormal biomarker measurements. This variable was coded as follows: 0-no abnormal biomarker measures; 1-abormal pancreastatin measurement only; 2-abnormal NKA measurement only; 3-abnormal serotonin measurement only; 4-abnormal 5-HIAA measurement only; 5-abnormal CgA measurement only; 6-abnormal gastrin measurement only; 7-2 abnormal biomarker measurements; and 8-3 or more abnormal biomarker measurements. For this variable, the 17 individuals with missing biomarker data were assigned the missing data code, 99. Once the Excel file was imported into SPSS version 23, the scores for the total QOL score and seven domain variables (depression, flushing, respiratory, gastrointestinal, cardiovascular, physical functioning, and attitude) were rechecked as well.

Results

Descriptive Statistics

There were a total of 134 patients in the QOL-NET dataset. Fifty-nine percent (59%; $n = 79$) of the population was female, which is notable because NETs appear to be more common in women than men in the United States (ACS, 2013). The average age of the population was 57.77 years. Additional demographic data for age can be found in Table 1. Data for race are in Table 2.

Table 1
Demographic Data for the QOL-NET Dataset Patients—Age

	Number of Patients	Percent
18-29 Years Group	3	2.2%
30-39 Years Group	7	5.2%
40-49 Years Group	24	17.9%
50-59 Years Group	37	27.6%
60-69 Years Group	42	31.3%
70-85 Years Group	17	12.7%
Missing	4	3.0%

Table 2
Demographic Data for the QOL-NET Dataset Patients—Race

	Number of Patients	Percent
Race—White	120	89.6%
Race—Black	9	6.7%
Race—Hispanic	2	1.5%
Race—White/Native American	2	1.5%
Missing	1	0.7%

Eighteen patients identified a family history of NETs. In the dataset, 129 patients responded to the demographics question that asked whether they have NET-related symptoms—65% of them responded "yes." Total QOL scores ranged from a low of 5 to a high of 230, with a mean score of 90.16. Appendix/small bowel and small bowel were the most common primary tumor sites, as seen in Table 3. Thirty-one (23.7%) of the patients had an unknown primary tumor site. For the purposes of the Research Question 1 analyses, primary tumor sites were grouped into larger organ systems, as noted above. The frequencies of the condensed primary tumor sites are shown in Table 4.

Table 3
Frequencies of Primary Tumor Sites in the QOL-NET Dataset

	Number of Patients	Percent
Appendix	7	5.3%
Appendix/Small Bowel	21	16.0%
Colon	5	3.8%
Duodenum	10	7.6%
Gastric	7	5.3%
Ileum	5	3.8%
Lung	9	6.9%
Other	4	3.1%
Pancreas	12	9.2%
Rectal	5	3.8%
Small Bowel	15	11.5%
Unknown	31	23.7%
Total	131	100%
Missing	3	

Table 4
Frequencies of Condensed Primary Tumor Sites in the QOL-NET Dataset

	Number of Patients	Percent
Appendix/Small Bowel	21	16.0%
Gastric	7	5.3%
Large Bowel	18	13.7%
Lung	9	6.9%
Other	3	2.3%
Pancreas	12	9.2%
Small Bowel	30	22.9%
Unknown	31	23.7%
Total	131	100%
Missing	3	

Biomarker data were available for 117 patients. Ninety-two (92) patients had at least one abnormal biomarker measurement. Of those 92 patients, 35 patients had one abnormal biomarker measurement only (38.0%), 27 patients had two abnormal

measurements (29.3%), and 30 patients had three or more abnormal biomarker measurements (32.6%). Twenty-five (25) patients didn't have any abnormal biomarker measurements. In this population, abnormal NKA measurements were not observed alone, but only in conjunction with other abnormal biomarker measurements. Table 5 shows the distribution of abnormal biomarker measurements in this population.

Table 5
Distribution of Abnormal Biomarker Measurements in the QOL-NET Dataset

	Number of Patients	Percent
No Abnormal Biomarker Measurement	25	21.4%
Abnormal Pancreastatin Measurement Only	5	4.3%
Abnormal Serotonin Measurement Only	8	6.8%
Abnormal 5-HIAA Measurement Only	3	2.6%
Abnormal CgA Measurement Only	17	14.5%
Abnormal Gastrin Measurement Only	2	1.7%
2 Abnormal Biomarker Measurements	27	23.1%
3 or More Abnormal Measurements	30	25.6%
Total	117	100%
Missing	17	

Table 6 shows whether or not individual biomarker measurements were normal for patients in the dataset. It should be noted that not every patient will express the same biomarkers, so missing data were expected.

Table 6
Whether or Not Biomarker Measurements are Normal in QOL-NET Patient Population

	Pancreastatin Normal	NKA Normal	Serotonin Normal	5-HIAA Normal	CgA Normal	Gastrin Normal
No	36 (41.4%)	6 (10.7%)	45 (54.2%)	22 (25.3%)	65 (65.7%)	17 (53.1%)
Yes	51 (58.6%)	50 (89.3%)	38 (45.8%)	65 (74.7%)	34 (34.3%)	15 (46.9%)
Total	87 (100%)	56 (100%)	83 (100%)	87 (100%)	99 (100%)	32 (100%)
Missing	47	78	51	47	35	102

Research Question 1

Research Question 1 and its hypotheses are as follows:

Research Question 1: What is the relationship between the primary tumor site and NET patients' total QOL score?

$H_0$1: There is no relationship between the primary tumor site and NET patients' total QOL score.

$H_1$1: There is a relationship between the primary tumor site and NET patients' total QOL score.

In Research Question 1, total QOL was the dependent variable and primary tumor site was the independent variable. The condensed version of the primary tumor site variable (referred to as "primary tumor site" henceforth), *Primary Tumor Site Condensed*, was used for these analyses. A one-way ANOVA was conducted followed by a post hoc test (Tukey HSD) to determine whether there were any significant differences in this patient population. Any results with a p-value less than 0.05 was considered significant. Separate one-way ANOVAs were conducted to determine whether there was a relationship between the following: total QOL (dependent variable) and age groups (independent variable; 18-29 years; 30-39 years; 40-49 years; 50-59 years; 60-69 years; and 70-85 years); total QOL and gender (independent variable; male and female); and total QOL and race (independent variable; white, black, and other). For these analyses, a Tukey HSD post hoc test was conducted where appropriate. Additionally, a multiple linear regression analysis was conducted to determine whether multiple independent variables (age, gender, race, and primary tumor site) affected total QOL. All of the independent variables were string variables and had to be recoded to run the multiple linear regression analysis in SPSS.

ANOVA results: Total QOL as the dependent variable. For a one-way ANOVA, it was assumed that data were independent, had equal variances, and were normally distributed. For the first ANOVA, total QOL (continuous) was the dependent variable. Primary tumor site (categorical) was the independent variable. The condensed version of the primary tumor site variable had eight categories: appendix/small bowel, gastric, large bowel, lung, other, pancreas, small bowel, and unknown. There were three missing data points in the primary tumor site variable. The ANOVA was not significant, F (8, 125) = 0.834, p = 0.575. The η^2 value indicated that primary tumor site only accounted for approximately 5.1% of the variance of total QOL. This result supported the null hypothesis that there is no relationship between primary tumor site and total QOL score. This result is discussed further in Chapter 5.

None of the related, additional one-way ANOVAs conducted for Research Question 1 were significant. Total QOL also served as the dependent variable for a one-way ANOVA where age groups were the independent variable. The age groups variable had six levels: 18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, and 70-85 years (there were 4 missing data points). The result for this analysis was not significant and can be seen in Table 7. The η2 value indicated that primary tumor site only accounted for 1.9% of the variance of total QOL score.

Table 7
One-Way ANOVA Results for Comparison of Total QOL and Age Groups

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	7359.84	6	1226.64	0.418	0.866	0.019
Within Groups	372337.76	127	2931.79			
Total	1468984.48	134				

Total QOL was the dependent variable for a one-way ANOVA where gender was the independent variable. Gender had two levels, female and male. The result for this analysis was not significant, as shown in Table 8. The η2 value indicated that primary tumor site only accounted for 2.3% of the variance of total QOL score.

Table 8
One-Way ANOVA Results for Comparison of Total QOL and Gender

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	8793.03	1	8793.03	3.129	0.079	0.023
Within Groups	370904.57	132	2809.88			
Total	1468984.48	134				

In the final one-way ANOVA for Research Question 1, total QOL was the dependent variable and race was the independent variable. Race had three levels: white, black, and other. The result for this analysis was not significant, as seen in Table 9. The η2 value indicated that primary tumor site only accounted for 1.1% of the variance of total QOL score.

Table 9
One-Way ANOVA Results for Comparison of Total QOL and Race

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	4307.54	2	2153.77	0.749	0.475	0.011
Within Groups	373790.97	130	2875.32			
Total	1452084.48	133				

Additional ANOVA results: QOL-NET domains as dependent variables.

Additional statistical tests related to this research question emerged during the analyses of these data. Specifically, these tests were intended to determine whether any of the individual domains of the QOL-NET (depression, flushing, respiratory, gastrointestinal, cardiovascular, physical functioning, and attitude) were affected by primary tumor site.

For each one-way ANOVA, one of the seven domains was treated as the dependent variable, and primary tumor site was the independent variable. Post hoc tests (Tukey HSD and Games-Howell) were conducted in SPSS to ascertain whether there were any significant differences and to control for potential Type I error. Any results with a p-value less than 0.05 were considered significant.

For the one-way ANOVA with the depression domain as the dependent variable and primary tumor site as the independent variable, results were not significant, as shown in Table 10. The η2 value indicated that primary tumor site only accounted for 7.3% of the variance of the domain score. The result from the one-way ANOVA with the flushing domain as the dependent variable and primary tumor site as the independent variable was not significant as well, as shown in Table 11. For this analysis, the η2 value indicated that primary tumor site only accounted for 3.9% of the variance of the domain score. The result from the one-way ANOVA with the respiratory domain as the dependent variable and primary tumor site as the independent variable was not significant (Table 12), and the η2 value indicated that primary tumor site only accounted for 9.2% of the variance of the domain score.

Table 10
One-Way ANOVA Results for Comparison of the Depression Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	991.81	8	123.978	1.230	0.287	0.073
Within Groups	12603.39	125	2875.32			
Total	50873.00	134				

Table 11
One-Way ANOVA Results for Comparison of the Flushing Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	225.21	8	28.15	0.632	0.750	0.039
Within Groups	5570.53	125	44.56			
Total	10348.68	134				

Table 12
One-Way ANOVA Results for Comparison of the Respiratory Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	571.77	8	71.47	1.576	0.139	0.092
Within Groups	5669.72	125	45.36			
Total	10284.00	134				

The one-way ANOVA for the next QOL-NET domain as the dependent variable (gastrointestinal) and primary tumor site as the independent variable was not significant (Table 13), and the η2 value indicated that primary tumor site only accounted for 4.0% of the variance of domain score. Table 14 (below) shows that the result from the one-way ANOVA with the cardiovascular domain as the dependent variable and primary tumor site as the independent variable was not significant as well. The η2 value for this analysis indicated that primary tumor site only accounted for 4.5% of the variance of domain score. Table 15 (below) shows that the result from the one-way ANOVA with the physical functioning domain as the dependent variable and primary tumor site as the independent variable was not significant. The η2 value indicated that primary tumor site only accounted for 6.3% of the variance of domain score. The final one-way ANOVA treated the attitude domain as the dependent variable and primary tumor site as the independent variable. Similar to the results of other one-way ANOVAs, this result was

not significant (Table 16), and the η2 value indicated that primary tumor site only accounted for 5.5% of the variance of domain score.

Table 13
One-Way ANOVA Results for Comparison of the Gastrointestinal Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	322.27	8	40.28	0.645	0.739	0.040
Within Groups	7808.12	125	62.47			
Total	21351.00	134				

Table 14
One-Way ANOVA Results for Comparison of the Cardiovascular Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	140.34	8	17.54	0.741	0.655	0.045
Within Groups	2959.79	125	23.68			
Total	4702.64	134				

Table 15
One-Way ANOVA Results for Comparison of the Physical Functioning Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	6548.32	8	818.54	1.058	0.397	0.063
Within Groups	96750.53	125	774.00			
Total	386207.63	134				

Table 16
One-Way ANOVA Results for Comparison of the Attitude Domain and Primary Tumor Site

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	55.03	8	6.88	0.902	0.518	0.055
Within Groups	938.51	123	7.63			
Total	2076.00	132				

Multiple linear regression analysis results. To conduct the multiple linear regression analysis, it was assumed that the data were measured reliably, were normally distributed, had equal variances, and that a linear relationship existed between the independent and dependent variables. All of the independent variables were string variables and had to be recoded to run the multiple linear regression analysis in SPSS. To recode these variables, the "Automatic Recode" feature was applied to the appropriate string variables in SPSS. Table 17 shows the recoded variables' new values, as assigned by SPSS.

Table 17
SPSS-Assigned New Values for Recoded String Variables

Original Value	New Value
Age: 18-29y	1
Age: 30-39y	2
Age: 40-49y	3
Age: 50-59y	4
Age: 60-69y	5
Age: 70-85y	6
Gender: Female	10
Gender: Male	14
Primary Tumor Site: Appendix/Small Bowel	8
Primary Tumor Site: Gastric	11
Primary Tumor Site: Large Bowel	12
Primary Tumor Site: Lung	13
Primary Tumor Site: Other	17
Primary Tumor Site: Pancreas	18
Primary Tumor Site: Small Bowel	19
Primary Tumor Site: Unknown	20
Race: White	21
Race: Black	9
Race: Other	16
Missing Data	23M

For the Research Question 1 multiple linear regression analysis, total QOL was the dependent variable. The predictors in this model were the recoded primary tumor site,

race, age groups, and gender variables. The predictors were not significantly related to total QOL, F (4, 125) = 1.116, p = 0.352. The R-squared (R^2) value was 0.034, indicating that only 3.4% of the variance was explained by this model (the adjusted R^2 = 0.004). Table 18 shows the predictor coefficients for this model, none of which were significant.

Table 18
Predictor Coefficients for Gender, Race, Age Groups, and Primary Tumor Site

	B	Standard Error	Standardized β	*p*-value
Age Groups	-0.273	3.770	-0.006	0.942
Gender	-4.523	2.421	-0.166	0.064
Race	-0.352	1.520	-0.021	0.817
Primary Tumor Site	0.982	1.057	0.083	0.354

Research Question 2

Research Question 2 and its hypotheses are as follows:

Research Question 2: How does the presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affect the total QOL score for NET patients?

$H_0$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) does not affect the total QOL score for NET patients.

$H_1$2: The presence of specific NET biomarkers (NKA, pancreastatin, serotonin, 5-HIAA, gastrin, and CgA) affects the total QOL score for NET patients.

In Research Question 2, a series of one-way ANOVAs and a multiple linear regression analysis were conducted to determine whether total QOL was affected by the presence of biomarkers. Post hoc tests (Tukey HSD and Games-Howell) were conducted

for the ANOVAs where appropriate. Any results with a p-value less than 0.05 were considered significant.

ANOVA results: Total QOL as the dependent variable. A categorical variable was created for Research Question 2, *Presence of Abnormal Biomarkers*. For the first one-way ANOVA, the presence of abnormal biomarker measurements was treated as an independent variable and total QOL was the dependent variable. This result was significant, suggesting that the presence of abnormal biomarkers may have a relationship with total QOL, as shown in Table 19. The η2 value indicated that the presence of abnormal biomarkers accounted for 15.0% of the variance of total QOL score, which is moderately strong.

Table 19
One-Way ANOVA Results for Comparison of Total QOL and Presence of Abnormal Biomarkers

	Sum of Squares	Df	Mean Square	*F*	*p*-value	η2
Between Groups	48104.53	7	6872.08	2.752	0.011*	0.150
Within Groups	272147.32	109	2496.76			
Total	1198996.91	117				

*$p < 0.05$

Since this analysis did not pass the Levene's Test of Equality of Error Variances (test for homogeneity of variances), the Games-Howell post hoc test was used instead of the Tukey HSD post hoc test. According to the results of the Games-Howell post hoc, there were significant differences between patients with an abnormal gastrin measurement only and the following groups: no abnormal biomarker measurement *(p* = 0.003); an abnormal serotonin measurement only (*p* = 0.032); an abnormal CgA

measurement only ($p = 0.003$); 2 abnormal biomarker measurements ($p = 0.000$); and 3 or more abnormal measurements ($p = 0.000$). Ultimately, the result of this ANOVA is supportive of the alternative hypothesis that the presence of specific NET biomarkers affected the total QOL score for NET patients.

Toward Research Question 2, I also examined each of the six *[Biomarker] Normal* variables as an independent variable with total QOL as the dependent variable using a one-way ANOVA to determine whether any individual biomarkers affected total QOL. In the one-way ANOVA for *Pancreastatin Normal*, the results were not significant, as shown below in Table 20 (η2 value indicated that this variable only accounted for 0.7% of the variance of total QOL score). The result of the one-way ANOVA for *NKA Normal* was also not significant, as seen in Table 21 (η2 value indicated that this variable only accounted for 0.1% of the variance of total QOL score).

Table 20
One-Way ANOVA Results for Comparison of Total QOL and the Pancreastatin Normal Variable

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	1580.72	1	1580.72	0.557	0.458	0.007
Within Groups	241223.98	85	2837.93			
Total	914893.91	87				

Table 21
One-Way ANOVA Results for Comparison of Total QOL and the NKA Normal Variable

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	88.60	1	88.60	0.030	0.863	0.001
Within Groups	157989.33	54	2925.73			
Total	567794.00	56				

The result of the one-way ANOVA for *5-HIAA Normal* was not significant as well (Table 22; η2 value indicated that this variable only accounted for 0.2% of the variance of total QOL score). The result of the one-way ANOVA for *CGA Normal* was also not significant, as shown in Table 23 (η2 value indicated that this variable only accounted for 0.4% of the variance of total QOL score). The one-way ANOVA result for *Gastrin Normal* did not reach a level of significance (Table 24; η2 value indicated that this variable only accounted for 0.2% of the variance of total QOL score).

Table 22
One-Way ANOVA Results for Comparison of Total QOL and the 5-HIAA Normal Variable

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	602.86	1	602.86	0.207	0.650	0.002
Within Groups	247606.19	85	2913.01			
Total	942594.29	87				

Table 23
One-Way ANOVA Results for Comparison of Total QOL and the CGA Normal Variable

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	1088.91	1	1088.91	0.407	0.525	0.004
Within Groups	259459.55	97	2674.84			
Total	1000976.91	99				

Table 24
One-Way ANOVA Results for Comparison of Total QOL and the Gastrin Normal Variable

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	198.03	1	198.03	0.064	0.801	0.002
Within Groups	92296.45	30	3076.55			
Total	368535.69	32				

In the one-way ANOVA for *Serotonin Normal*, the results were significant and can be seen in Table 25 (η2 value indicated that this variable only accounted for 11.7% of the variance of total QOL score). Since there were only two levels in the independent variable, a post hoc test was not necessary. This was the only significant finding in the one-way ANOVA analyses for the series of *[Biomarker] Normal* variables.

Table 25
One-Way ANOVA Results for Comparison of Total QOL and Presence of Abnormal Biomarkers

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	26379.73	1	26379.73	10.757	0.002*	0.117
Within Groups	198644.11	81	2452.40			
Total	887065.75	83				

*$p < 0.05$

Additional ANOVA results: QOL-NET domains as dependent variables.

Additional statistical tests related to Research Question 2 emerged during the analyses of these data. Specifically, these tests were intended to determine whether any of the individual domains of the QOL-NET (depression, flushing, respiratory, gastrointestinal, cardiovascular, physical functioning, and attitude) were affected by the presence of abnormal biomarker measurements. For each one-way ANOVA, one of the seven domains was treated as the dependent variable, and the presence of abnormal biomarker measurements was maintained as the independent variable. Post hoc tests (Tukey HSD and Games-Howell) were conducted to ascertain whether there were any significant differences. Any results with a p-value less than 0.05 were considered significant.

With the exception of the one-way ANOVAs for the gastrointestinal and physical functioning domains, none of the other results were significant. The result of the one-way ANOVA with the gastrointestinal domain as the dependent variable and presence of abnormal biomarker measurements as the independent variable was significant—this result is shown in Table 26 (η2 value indicated that this variable accounted for 16.8% of the variance of the domain score).

Table 26
One-Way ANOVA Results for Comparison of the Gastrointestinal Domain and Presence of Abnormal Biomarkers

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	1144.36	7	163.48	3.139	0.005*	0.168
Within Groups	5676.53	109	52.08			
Total	17504.00	117				

*$p < 0.05$

Since this analysis did not pass the Levene's Test of Equality of Error Variances (test for homogeneity of variances), the Games-Howell post hoc test was used instead of the Tukey HSD post hoc test. According to the results of the Games-Howell post hoc, there were significant differences between patients with an abnormal CgA measurement only and patients with 2 abnormal biomarker measurements ($p = 0.006$).

The result of the one-way ANOVA with the physical functioning domain as the dependent variable and presence of abnormal biomarker measurements as the independent variable was also significant (shown in Table 27; η2 value indicated that this variable accounted for 13.0% of the variance of the domain score).

Table 27
One-Way ANOVA Results for Comparison of the Physical Functioning Domain and Presence of Abnormal Biomarkers

	Sum of Squares	df	Mean Square	*F*	*p*-value	η2
Between Groups	11070.98	7	1581.57	2.319	0.030*	0.130
Within Groups	74335.58	109	681.98			
Total	310959.63	117				

*$p < 0.05$

Since this analysis also did not pass the Levene's Test of Equality of Error Variances (test for homogeneity of variances), the Games-Howell post hoc test was used instead of the Tukey HSD post hoc test. According to the results of the Games-Howell post hoc, there were significant differences between patients with an abnormal gastrin measurement and the following groups: patients with no abnormal biomarker measurement ($p = 0.005$); patients with an abnormal serotonin measurement only ($p = 0.010$); patients with an abnormal 5-HIAA measurement only ($p = 0.042$); patients with an abnormal CgA measurement only ($p = 0.021$); patients with 2 abnormal biomarker measurements ($p = 0.000$); and patients with 3 or more abnormal measurements ($p = 0.002$).

Multiple linear regression analysis. For this research question, a multiple linear regression analysis was conducted to determine whether multiple independent variables (age, gender, race, and presence of abnormal biomarker measurements) affected total QOL. As noted earlier in the chapter, the independent variables age, gender, and race were string variables and had to be recoded to run the multiple linear regression analysis in SPSS. To recode these variables, the "Automatic Recode" feature was applied to the

appropriate string variables in SPSS.

The predictors were not significantly related to total QOL, F (4, 111) = 1.514, p = 0.203. The R^2 value was 0.052, indicating that only 5.2% of the variance was explained by this model (the adjusted R^2 = 0.018). Table 28 shows the predictor coefficients for this model.

Table 28
Predictor Coefficients for Gender, Race, Age Groups, and Presence of Abnormal Biomarker Measurements

	B	Standard Error	Standardized β	*p*-value
Age Groups	-3.921	3.946	-0.093	0.323
Gender	-4.891	2.498	-0.185	0.053
Race	0.489	1.437	0.032	0.734
Abnormal Biomarker Presence	1.371	1.605	0.081	0.395

Gender almost reached a level of significance as a predictor (p=0.053), which led to another linear regression model with gender and presence of abnormal biomarker measurements as predictors for total QOL. The result for this second regression analysis was not significant, F (2, 114) = 2.345, p = 0.100. The R^2 value was 0.040, indicating that only 4.0% of the variance was explained by this model (the adjusted R^2 = 0.023). Table 29 shows the predictor coefficients for this model.

Table 29
Predictor Coefficients for Gender and Presence of Abnormal Biomarker Measurements

	Unstandardized Coefficients		Standardized Coefficient		
	B	Standard Error	Beta	t-statistic	Significance
Constant	147.920	38.179		3.874	0.000
Gender	-4.576	2.445	-0.173	-1.871	0.064
Biomarker Presence	1.282	1.570	0.076	0.817	0.416

Summary

None of the results from the one-way ANOVAs for Research Question 1 were significant; thus, they supported the null hypothesis that there is no relationship between total QOL and primary tumor site. Results from the analyses for Research Question 2 showed that the presence of abnormal biomarker measurements may affect total QOL. Additionally, it appeared that abnormal serotonin measurements may impact total QOL. The gastrointestinal and physical functioning domains also appear to be affected by the presence of abnormal biomarker measurements. An interpretation of the findings from this study is included in Chapter 5 along with study limitations, recommendations, and implications for this research.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

This study was conducted to examine the relationship between NET patients' total QOL score and their primary tumor sites in addition to assessing the relationship between total QOL and novel biomarkers of the disease. For the purpose of this quantitative study, secondary data from a NET patient database from Eastern Virginia Medical School were evaluated. Although the results indicated that there was no relationship between primary tumor site and NET patients' total QOL score, it does appear that the presence of abnormal biomarker measurements affected total QOL score. These findings are discussed in this chapter along with the study's limitations, recommendations, and implications.

Interpretation of the Findings

Over half of the patients (65%) in the QOL-NET database responded that they had NET-related symptoms. This population's total QOL scores ranged from 5.00 to 230.00, with a mean total QOL score of 90.16 (SD ± 53.43). While 59% of the dataset population was female, there were no significant differences between the total QOL scores of female and male patients (F (1,32) = 3.129, p = 0.079). As reported in Chapter 4, age, race, and gender did not affect total QOL. Almost a quarter (23.7%) of the patients in this dataset had unknown primary tumor sites, which is not unexpected for NETs.

Research Question 1 inquired about the relationship between the primary tumor site and NET patients' total QOL score. Results from the analyses supported the null

hypothesis—there was no relationship between primary tumor site and the total QOL score, even when the primary tumor sites were condensed into their larger organ groups when possible for analytical purposes (F (8, 125) = 0.834, p = 0.575). It is possible that the wide range of primary tumor sites and limited number of patients in each group affected the analysis. Furthermore, primary tumor sites did not have a relationship with any of the seven domains in the QOL-NET (depression, flushing, respiratory, gastrointestinal, cardiovascular, physical functioning, and attitude). As part of this research question, a multiple linear regression analysis was conducted to ascertain whether multiple independent variables affected total QOL, but the result was not significant.

In the analyses for Research Question 2, there were significant results that supported the alternative hypothesis: the presence of specific NET biomarkers affected the total QOL score for NET patients in this population. These results also contributed to the body of knowledge about how biomarkers and NETs affect patients' QOL, and they warrant further study. In the analysis with the independent categorical variable created for Research Question 2, *Presence of Abnormal Biomarkers*, the results of the one-way ANOVA showed that the presence of abnormal biomarker measures affected total QOL (p = 0.011) for these patients. Specifically, there appeared to be significant differences between patients who only had abnormal gastrin measurements and five other categories: no abnormal biomarker measurement (p = 0.003); an abnormal serotonin measurement only (p = 0.032); an abnormal CgA measurement only (p = 0.003); 2 abnormal biomarker measurements (p = 0.000); and 3 or more abnormal measurements (p = 0.000). This

finding is noteworthy because there is less information about gastrin as a biomarker for NETs; consequently, it is known that it can be a biomarker for a variety of NETs, including those in the bronchus, pancreas, stomach, and duodenum (Modlin et al., 2008). CgA and serotonin are widely studied NETs biomarkers, and they have been associated with QOL previously (Ardill & Erikkson, 2003; Eriksson et al., 2000; Korse et al., 2009; Modlin et al., 2008; A. Vinik et al., 2009). CgA was associated with a common NET patients' symptom (diarrhea) in an earlier study (Larsson et al., 2001). In another study, CgA correlated significantly with overall QOL and physical functioning (Korse et al., 2009). Serotonin correlated significantly with total QOL from the two NET-specific QOL instruments and three domains from the QOL-NET (physical functioning, depression, and gastrointestinal) previously as well (Vinik et al., 2014).

The presence of abnormal biomarker measurements significantly affected the gastrointestinal domain ($p = 0.005$) and physical functioning domain ($p = 0.030$). According to the post hoc test for the gastrointestinal domain, there were significant differences between patients with an abnormal CgA measurement only and patients with 2 abnormal biomarker measurements ($p = 0.006$). This is interesting because it is known that CgA is secreted in gastrointestinal NETs and other tumor subtypes (Prestifilippo et al., 2012). It has also been referred to as an important biomarker for diagnosing and managing gastroenteropancreatic NETs (Lawrence, Gustafsson, & Kidd, et al., 2011). For the analysis with the physical functioning domain, the post hoc test indicated that there were significant differences between patients with an abnormal gastrin measurement and the following groups: patients with no abnormal biomarker measurement ($p = 0.005$);

patients with an abnormal serotonin measurement only ($p = 0.010$); patients with an abnormal 5-HIAA measurement only ($p = 0.042$); patients with an abnormal CgA measurement only ($p = 0.021$); patients with 2 abnormal biomarker measurements ($p = 0.000$); and patients with 3 or more abnormal measurements ($p = 0.002$). Since physical functioning contributes the most to total QOL in the QOL-NET, it is not surprising that the post hoc results were similar to those in an earlier study (E. Vinik et al., 2009).

In the analyses of whether the independent *[Biomarker] Normal* variables affected the dependent total QOL variable, only the result for *Serotonin Normal* was significant ($p = 0.002$). It appears that the serotonin biomarker affected QOL for NET patients in this study population. This finding supported previous research that found a significant correlation between serotonin and three of the QOL-NET domains (physical functioning, gastrointestinal, and depression) as well as a significant correlation between serotonin and total QOL (Vinik et al., 2011; Vinik et al., 2014).

With regards to this study's theoretical framework, the explanatory model of health promotion and quality of life in chronic disabling conditions, the total QOL scores alone showed that QOL is impacted by NETs (Stuifbergen et al., 2000). The findings from Research Question 2 aligned with the theoretical framework—there were different, independent factors that affected QOL either directly or indirectly (Stuifbergen et al., 2000). QOL is a multidimensional construct, and the presence of certain NET biomarkers is likely one of many independent factors that affected total QOL for these NET patients. Knowing this can help answer the *how* and *why* aspects of QOL for these individuals living with this disease.

Limitations of the Study

The results of this study are limited to adult patients with NETs ranging from 18 to 85 years of age. It did not appear that age was a limitation in the study, but most patients were between 40-69 years of age (mean age 57.77 ± 13.64 years). It has been reported elsewhere that race is a risk factor for NETs, but this patient population was predominantly white (90%), so I was unable to determine if race was a factor that affected their total QOL scores (ACS, 2013). Race was not a significant predictor in any of the multiple linear regression analyses.

There were data available for 134 patients in this dataset, which may have been a limiting factor. It is possible that more significant results would have been found in a larger study population. Within the dataset, there were 41 patients who had skipped at least one question in the QOL-NET. Skipped questions affected total QOL scores as well as domain scores and could have introduced self-report bias to the results. Although the Norfolk QOL-NET's reliability and validity helped avoid instrumentation limitations, there were instances where an analysis did not pass a test for homogeneity of variances, a statistical assumption for an ANOVA. (Within the primary tumor site and presence of abnormal biomarker measurements, there were unequal sample sizes.) To offset this issue, the Games-Howell post hoc test was conducted because it is meant for unequal sample sizes and variances.

Information about how the patients in the clinic were different from other patients was not available, which could be considered an additional limitation. Related to this limitation, I did not have information about whether or not the patients were referred

there, and it was unknown how the patients who agreed to participate were different from those who did not.

Recommendations

It may be difficult to distinguish statistical differences in total QOL scores among NET patients with different primary tumor sites because this disease has such an impact on their QOL. It is also possible that a larger study population is needed with more patients in each primary tumor site group to detect a significant difference. As Lawrence, Gustafsson, Chan, et al.'s (2011) observed, "There is a distinct epidemiologic profile for each primary site" (p. 16). It would be worthwhile to conduct similar analyses in a larger patient population. It could also be valuable to evaluate the QOL scores of this NET patient population against the QOL scores of a comparable healthy population, as other studies have demonstrated that NET patients have worse QOL scores than the general population (Fröjd et al., 2007; Haugland et al., 2013; Larsson et al., 2001; E. Vinik et al., 2009; Vinik et al., 2011; Vinik et al., 2014; Yadegarfar et al., 2013). Based on findings that NET biomarkers affected total QOL and measurable QOL domains (i.e., the physical functioning and gastrointestinal domains of the QOL-NET), further studies about domain-specific aspects of QOL and NET-specific biomarkers (i.e., gastrin, serotonin, or CgA) are warranted. Additionally, in future studies (or even a clinical setting), physicians may want to monitor patient-reported outcomes closely for NET patients who have 2 or more abnormal biomarker measurements, as it is possible that those biomarkers are responsible for disease-related symptoms that can challenge patients' QOL (Haugland et al., 2013; Kulke et al., 2011; Modlin et al., 2008; Öberg & Castellano, 2011).

Implications

It is clear from this study that NETs affected patients' QOL, regardless of the primary tumor site. Results from Research Question 2 contributed new data to the small yet growing body of knowledge about the relationship between NET biomarkers and patients' QOL. Patients, caretakers, and physicians can use that information to develop approaches to maintaining and improving patients' QOL throughout their illness. Doing so would be a positive social change for this patient population and their caretakers/family members. Additionally, this study can be used to support the need for further research into the relationship of NET biomarkers and NET patients' QOL. Supporting additional research and work that can ultimately help NET patients has the potential to make a positive social change on a number of communities, from researchers to patients.

The results also reinforced previous findings about the association between the serotonin biomarker and total QOL in addition to providing insight into other biomarkers like gastrin (Vinik et al., 2011; Vinik et al., 2014). This information could be used by physicians to help NET patients who have abnormal serotonin measurements improve their well-being. This study also showed that abnormal biomarker measurements affected the gastrointestinal and physical functioning QOL domains. Through further research, physicians, patients, and caretakers can gain a better understanding of which aspects of QOL they can focus on to reduce the effects of specific biomarkers, which could make a positive impact on NET patients' lives. Contributing to the improvement of NET

patients' well-being through knowledge was a goal of this study, and it is believed that positive social change can happen based on these results.

Conclusion

NETs are a rare, complicated collection of neoplasms that are difficult to diagnose and treat. Furthermore, NETs are known to affect patients' QOL and the measurable domains that comprise this patient-reported outcome. The results from this study contribute to NET research by filling gaps in knowledge about QOL and NETs. Although the research results did not demonstrate that there is a relationship between primary tumor sites and total QOL, the results do demonstrate that there is a relationship between the presence of abnormal biomarker measurements and total QOL. Specifically, the results further support the relationship between serotonin and NET patients' total QOL in addition to demonstrating that specific NETs biomarkers may directly affect the gastrointestinal and physical functioning QOL domains within the Norfolk QOL-NET. Based on these findings, further research that facilitates a better understanding of NET biomarkers and their relationship to all aspects of patient QOL is warranted. Ultimately, the results from this study supported the literature about NET biomarkers' unique effects on patients' QOL, and they contributed to the information about the way NETs can impact individuals with the disease.

References

American Cancer Society. (2013). Gastrointestinal carcinoid tumors. Retrieved from http://www.cancer.org/acs/groups/cid/documents/webcontent/003102-pdf.pdf

Ardill, J. E., & Erikkson, B. (2003). The importance of the measurement of circulating markers in patients with neuroendocrine tumours of the pancreas and gut. *Endocrine-Related Cancer, 10,* 459-462. doi:10.1677/erc.0.0100459

Bostwick, D. G., Roth, K. A., Evans, C. J., Barchas, J. D. , & Bensch, K.G. (1984). Gastrin-releasing peptide, a mammalian analog of bombesin, is present in human neuroendocrine lung tumors. *American Journal of Pathology, 117*(2), 195-200. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1900454/

Burkitt, M. D., Varro, A., Pritchard, D. M. (2009). Importance of gastrin in the pathogenesis and treatment of gastric tumors. *World Journal of Gastroenterology, 15*(1), 1-16. doi:10.3748/WJG.15.1

Centers of Disease Control and Prevention. (2011, March 17). HRQOL concepts. Retrieved from http://www.cdc.gov/hrqol/concept.htm

Cummins, R. A. (2005). Moving from the quality of life concept to a theory. *Journal of Intellectual Disability Research, 49*(10), 699-706. doi:10.1111/j.1365-788.2005.00738.x

Davies, A. H., Larsson, G., Ardill, J., Friend, E., Jones, L., Falconi, M.,…Ramage J. K. (2006). Development of a disease-specific quality of life questionnaire module for patients with gastrointestinal neuroendocrine tumours. *European Journal of Cancer, 42*(4), 477-484. doi:10.1016/j.ejca.2005.10.025

Davis, N. (2009). Measuring health-related quality of life in cancer patients. *Nursing Standard, 23*(30), 42-49. Retrieved from http://www.academia.edu/317915/Measuring_Health-Related_QoL_in_Oncology

Diebold, A. E., Boudreaux, J. P., Wang, Y. Z., Anthony, L. B., Uhlhorn, A. P., Ryan, P.,…Woltering, E. A. (2012). Neurokinin A levels predict survival in patients with stage IV well differentiated small bowel neuroendocrine neoplasms. *Surgery, 152*(6), 1172-1176. doi:10.1016/j.surg.2012.08.057

Dobson, R., Burgess, M. I., Banks, M., Pritchard, D. M., Vora, J., Valle, J. W.,…Cuthbertson, D. J. (2013). The association of a panel of biomarkers with the presence and severity of carcinoid heart disease: A cross-sectional study. *PLoS One, 8*(9), e73679. doi:10.1371/journal.pone.0073679

Eriksson, B., Öberg, K., & Stridsberg, M. (2000). Tumor markers in neuroendocrine tumors. *Digestion, 62*(Supp. 1), 33-38. doi:10.1159/000051853

Fröjd, C., Larsson, G., Lampic, C., & von Essen, L. (2007). Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. *Health and Quality of Life Outcomes, 5*, 18. doi:10.1186/1477-7525-5-18

Gilbert, J. A., Adhikari, L. J., Lloyd, R. V., Rubin, J., Haluska, P., Carboni, J. M.,…Ames, M. M. (2010). Molecular markers for novel therapies in neuroendocrine (carcinoid) tumors. *Endocrine-Related Cancer, 17,* 623-636. doi:10.1677/ERC-09-0318

Green, J. (2000). The role of theory in evidence-based health promotion practice. *Health*

Education Research, 15(2), 125-129. doi:10.1093/her/15.2.125

Haugland, T., Vatn, M. H., Veenstra, M., Wahl, A. K., & Natvig, G. K. (2009). Health related quality of life in patients with neuroendocrine tumors compared with the general Norwegian population. *Quality of Life Research, 18*(6), 719-726. doi: 10.1007/s11136-009-9487-x

Haugland, T., Veenstra, M., Vatn, M. H., & Wahl, A. K. (2013). Improvement in stress, general self-efficacy, and health related quality of life following patient education for patients with neuroendocrine tumors: A pilot study. *Nursing Research and Practice, 2013.* doi:10.1155/2013/695820

Hauso, O., Gustafsson, B. I., Kidd, M., Waldum, H. L., Drozdov, I., Chan, A. K., & Modlin, I. M. (2008). Neuroendocrine tumor epidemiology: Contrasting Norway and North America. *Cancer, 113*(10), 2655-2664. doi:10.1002/cncr.23883

Hijioka, M., Ito, T., Igarashi, H., Fujimori, N., Lee, L., Nakamura, T.,…Takayanagi, R. (2014). Serum chromogranin A is a useful marker for Japanese patients with pancreatic neuroendocrine tumors. *Cancer Science, 105*(11), 1464-1471. doi:10.1111/cas/12533

Hocker, M. (2004). Molecular mechanisms of gastrin-dependent gene regulation. *Annals of the New York Academy of Sciences, 1014*, 97-109. doi:10.1196/annals.1294.010

Ito, T., Igarashi, H., & Jensen, R. T. (2012). Serum pancreastatin: The long sought for universal, sensitive, specific tumor marker for neuroendocrine tumors (NETs). *Pancreas, 41*(4), 505-507. doi:10.1097/MPA.0b013e318249a92a

Jann, H., Roll, S., Couvelard, A., Hentic, O., Pavel, M., Müller-Nordhorn, J.,…Pape, U.F. (2011). Neuroendocrine tumors of midgut and hindgut origin: Tumor-node-metastasis classification determines clinical outcome. *Cancer, 117*(15), 3332-3341. doi:10.1002/cncr.25855

Kawamoto, S., Shi, C., Hruban, R. H., Choti, M. A., Schulick, R. D., Fishman, E. K., & Siegelman, S. S. (2011). Small serotonin-producing neuroendocrine tumor of the pancreas associated with pancreatic duct obstruction. *American Journal of Roentgenology, 197*(3), W482-W488. doi:10.2214/AJR.10.5428

Keiser, J., Bergsland, E., & Nakakura, E. (2012). Chapter 4: The diagnosis and management of neuroendocrine carcinoma of unknown primary. In A. Lowell (Ed.), *Neuroendocrine Tumor* (37-46). Rijeka, Croatia: InTech.

Kleinman, A., Eisenberg, L., & Good, B. (1978). Culture, illness, and care: Clinical lessons from anthropology and cross-cultural research. *Annals of Internal Medicine, 88,* 251-258. doi:10.7326/0003-4819-88-2-251

Klöppel, G. (2007). Tumor biology and histopathology of neuroendocrine tumors. *Best Practice & Research Clinical Endocrinology & Metabolism, 21*(1), 15-31. doi:10.1016/j.beem.2007.01.004

Klöppel, G. & Clemens, A. (1996). The biological relevance of gastric neuroendocrine tumors. *Yale Journal of Biology and Medicine, 69*, 69-74. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2588971/pdf/yjbm00031-0072.pdf

Korse, C. M., Bonfrer, J. M., Aaronson, N. K., Hart, A. A., & Taal, B. G. (2009).

Chromogranin A as an alternative to 5-hydroxyindoleacetic acid in the evaluation of symptoms during treatment of patients with neuroendocrine tumors. *Neuroendocrinology, 89*(3), 296-301. doi:10.1159/000162876.

Knox, C. D., Feurer, I. D., Wise, P. E., Lamps, L. W., Wright, J. K., Chari, R. S.,…Pinson, C. Q. (2004). Survival and functional quality of life after resection for hepatic carcinoid metastasis. *Journal of Gastrointestinal Surgery, 8*(6), 653-659. doi:10.1016/j.gassur.2004.04.003

Kulke, M. H., Siu, L. L., Tepper, J. E., Fisher, G., Jaffe, D., Haller, D. G.,…Yao, J. C. (2011). Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. *Journal of Clinical Oncology, 29*(7), 934-943. doi:10.1200/JCO.2010.33.2056

Larsson, G., Sjödén, P. O., Öberg, K., Eriksson, B., & von Essen, L. (2001). Health-related quality of life, anxiety and depression in patients with midgut carcinoid tumours. *Acta Oncologica, 40*(7), 825-831. doi:10.1080/02841860152703445

Larsson, G., von Essen, L., & Sjödén, P.O. (1998). Quality of life in patients with endocrine tumors of the gastrointestinal tract: Patient and staff perceptions. *Cancer Nursing (21)*6, 411-420. Retrieved from http://journals.lww.com/cancernursingonline/Abstract/1998/12000/Quality_of_life_in_patients_with_endocrine_tumors.5.aspx

Lawrence, B., Gustafsson, B. I., Chan, A., Svedja, B., Kidd, M., & Modlin, I. M. (2011). The epidemiology of gastroenteropancreatic neuroendocrine tumors.

Endocrinology and Metabolism Clinics of North America, 40, 1-18. doi:10.1016/j.ecl.2010.12.005

Lawrence, B., Gustaffson, B. I., Kidd, M., Pavel, M., Svedja, B., & Modlin, I. M. (2011). The clinical relevance of chromogranin A as a biomarker for gastroenteropancreatic neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America, 40*, 111-134. doi:10.1016/j.ecl.2010.12.001

Lee, C. G., Lim, Y. J., Park, S. J., Jang, B. I., Choi, S. R., Kim, J. K.,…Song, S. Y. (2014). The clinical features and treatment modality of esophageal neuroendocrine tumors: A multicenter study in Korea. *BMC Cancer, 14*, 569. doi:10.1186/1471-2407-14-569

Mamikunian, P., Ardill, J .E., O'Dorisio, T. M., Krutzik, S. R., Vinik, A.I., Go, V. L.,…Woltering, E. A. (2011). Validation of neurokinin A assays in the United States and Europe. *Pancreas, 40*(7), 1000-1005. doi:10.1097/MPA.0b013e318232b6a2

Mayo Clinic. (2013, June 27). *Neuroendocrine tumors.* Retrieved from http://www.mayoclinic.org/diseases-conditions/neuroendocrine-tumors/basics/definition/con-20036333

Metz, D. C., & Jensen, R. T. (2008). Gastrointestinal neuroendocrine tumors: Pancreatic endocrine tumors. *Gastroenterology, 135*(5), 1469-1492. doi:10.1053/j.gastro.2008.05.047

Modlin, I. M., Gustafsson, B. I., Moss, S. F., Pavel, M., Tsolakis, A. V., & Kidd, M. (2010). Chromogranin A--Biological function and clinical utility in neuro

endocrine tumor disease. *Annals of Surgical Oncology, 17*(9), 2427-2443. doi: 10.1245/s10434-010-1006-3

Modlin, I. M., Öberg, K., Chung, D. C., Jensen, R. T., de Herder, W. W., Thakker, R. V.,…Sundin, A. (2008). Gastroenteropancreatic neuroendocrine tumors. *Lancet Oncology, 9*(1)*,* 61-72. doi:10.1016/S1470-2045(07)70410-2

National Cancer Institute. (n.d.). *NCI dictionary of cancer terms.* Retrieved from http://www.cancer.gov/dictionary?cdrid=653117

National Cancer Institute. (2005). *Theory at a glance: A guide for health promotion practice* (2nd ed.). Retrieved from http://www.cancer.gov/cancertopics/cancerlibrary/theory.pdf

Öberg, K., & Castellano, D. (2011). Current knowledge on diagnosis and staging of neuroendocrine tumors. *Cancer and Metastasis Reviews, 30*(Suppl 1), S3-S7. doi:10.1007/s10555-011-9292-1

Öberg, K., Knigge, U., Kwekkeboom, D., & Perren, A. (2012). Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology, 23*(Supp. 7), vii124–vii130. doi:10.1093/annonc/mds295

Ormel, J., Lindenberg, S., Steverink, N., & Vonkorff, M. (1997). Quality of life and social production functions: A framework for understanding health effects. *Social Science & Medicine, 45*(7), 1051-1063. doi:10.1016/S0277-9536(97)00032-4

Phillips, L. J. (2005). Analysis of the explanatory model of health promotion and QOL in chronic disabling conditions. *Rehabilitation Nursing, 30*(1), 18-24.

doi:10.1002/j.2048-7940.2005.tb00348.x

Prestifilippo, A., Blanco, G., Vitalo, M. P., & Giuffrida, D. (2012). Chapter 2: Chromogranin A and neuroendocrine tumors. In A. Lowell (Ed.), *Neuroendocrine Tumor* (11-18). Rijeka, Croatia: InTech.

Raosoft, Inc. (2004). Sample size calculator. Retrieved August 15, 2015, from http://www.raosoft.com/samplesize.html

Seregni, E., Ferrari, L., Bajetta, E., Martinetti, A., & Bombardieri, E. (2001). Clinical significance of blood chromogranin A measurement in neuroendocrine tumours. *Annals of Oncology, 12*(Supp. 2), S69-S72. doi: 10.1093/annonc/12.suppl_2.S69

Stuifbergen, A. K., Seraphine, A., & Roberts, G. (2000). An explanatory model of health promotion and quality of life in chronic disabling conditions. *Nursing Research, 49*(3), 122-129. Retrieved from http://journals.lww.com/nursingresearchonline/pages/articleviewer.aspx?year=2000&issue=05000&article=00002&type=abstract

Tellez, M. R., Mamikunian, G., O'Dorisio, T. M., Vinik, A. I., Woltering, E. A. (2013). A single fasting plasma 5-HIAA value correlates with 24-hour urinary 5-HIAA values and other biomarkers in midgut neuroendocrine tumors (NETs). *Pancreas, 42*(3), 405-410. doi:10.1097/MPA.0b013e318271c0d5

Tsikitis, V. L., Wertheim, B. C., & Guerrero, M. A. (2012). Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: A SEER analysis. *Journal of Cancer, 3*, 292-302. doi:10.7150/jca.4502

Turaga, K. K., & Kvols, L. K. (2011). Recent progress in the understanding, diagnosis,

and treatment of gastroenteropancreatic neuroendocrine tumors. *CA: A Cancer Journal for Clinicians, 61*(2), 113-132. doi:10.3322/caac.20097

Turner, G. B., Johnston, B. T., McCance, D. R., McGinty, A., Watson, R. G. P., Patterson, C. C., & Ardill, J. E. S. (2006). Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours. *Gut*, *55*(11), 1586–1591. doi:10.1136/gut.2006.092320

Van der Horst-Schrivers, A. N., Post, W. J., Kema, I. P., Links, T. P., Willemse, P. H., Wymenga, A. N., & de Vries, E. G. (2007). Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumours. *European Journal of Cancer, 43*(18), 2651-2657. doi:http://dx.doi.org/10.1016/j.ejca.2007.07.025

Van Eeden, S., Quaedvlieg, P. F., Taal, B. G., Offerhaus, G. J., Lamers, C. B., & Van Velthuysen, M. L. (2002). Classification of low-grade neuroendocrine tumors of midgut and unknown origin. *Human Pathology, (33)*11, 1126-1132. doi: http://dx.doi.org/10.1053/hupa.2002.129204

Vinik, A. I., & Gonzales, M. R. C. (2011). New and emerging syndromes due to neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America, 40*(1), 19-63. doi:10.1016/j.ecl.2010.12.010

Vinik, A. I., Silva, M. P., Woltering, E. A., Go, V. L., Warner, R., & Caplin, M. (2009). Biochemical testing for neuroendocrine tumors. *Pancreas, 38*(8), 876-889. doi:10.1097/MPA.0b013e3181bc0e77

Vinik, A. I., Vinik, E., Diebold, A., & Woltering, E. (2014). Chapter 14: Measuring the

relationship of quality of life and health status: Including tumor burden, symptoms, and biochemical measures in patients with neuroendocrine tumors. In E. Raymond, S. Faivre, & P. Ruszniewski (Eds.), *Management of neuroendocrine tumors of the pancreas and digestive tract* (pp. 199-220). France: Springer-Verlag.

Vinik, E., Carlton, C. A., Silva, M. P., & Vinik, A. I. (2009). Development of the Norfolk quality of life tool for assessing patients with neuroendocrine tumors. *Pancreas, 38*(3), e87-e95. doi:10.1097/MPA.0b013e31819b6441

Vinik, E., Silva, M. P., & Vinik, A. I. (2011). Measuring the relationship of quality of life and health status, including tumor burden, symptoms, and biochemical measures in patients with neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America, 40,* 97-109. doi:10.1016/j.ecl.2010.12.008

Yadegarfar, G., Friend, L., Jones, L., Plum, L. M., Ardill, J., Taal, B.,…Ramage, J. K. (2013). Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life in patients with gastrointestinal neuroendocrine tumors. *British Journal of Cancer, 108*(2), 301-310. doi:10.1038/bjc.2012.560

Zhang, J., Jia, Z., Li, Q., Wang, L., Rashid, A., Zhu, Z.,…Yao, J. C. (2007). Elevated expression of vascular endothelial growth factor correlates with increased angiogenesis and decreased progression-free survival among patients with low-grade neuroendocrine tumors. *Cancer, 109*, 1478-1486. doi:10.1002/cncr.22554

Appendix A: Data Use Agreement

DATA USE AGREEMENT

This Data Use Agreement ("Agreement"), effective as of October 1, 2015 ("Effective Date"), is entered into by and between Stephanie Ford-Scheimer ("Data Recipient") and Dr. Aaron and Mrs. Etta Vinik ("Data Provider"). The purpose of this Agreement is to provide Data Recipient with access to a Limited Data Set ("LDS") for use in research **in accord with laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.** In the case of a discrepancy among laws, the agreement shall follow whichever law is more strict.

1. Definitions. Due to the study's affiliation with Laureate, a USA-based company, unless otherwise specified in this Agreement, all capitalized terms used in this Agreement not otherwise defined have the meaning established for purposes of the USA "HIPAA Regulations" and/or "FERPA Regulations" codified in the United States Code of Federal Regulations, as amended from time to time.

2. Preparation of the LDS. Data Provider shall prepare and furnish to Data Recipient a LDS in accord with any applicable laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.

3. Data Fields in the LDS. **No direct identifiers such as names may be included in the Limited Data Set (LDS).** In preparing the LDS, Data Provider shall include the **data fields specified as follows**, which are the minimum necessary to accomplish the research related to the Norfolk QOL-NET instrument and biomarker data: Patient ID; Gender; Race; Have you been told you have carcinoid; Do you have an endocrine tumor; Family History; Lost weight; High BP; Symptoms; Flushing; Hot; Sweat; Q1; Q2; Q3; Q4; Q5; Q6; Q7; Q8; Q9; Q10; Q11; Q12; Q13; Q14; Q15; Q16; Q17; Q18; Q19; Q20; Q21; Q22; Q23; Q24; Q25; Q26; Q27; Q28; Q29; Q30; Q31; Q32; Q33; Q34; Q35; Q36; Q37; Q38; Q39; Q40; Q41; Q42; Q43; Q44; Q45; Q46; Q47; Q48; Q49; Q50; Q51; Q52; Q53; Q54; Q59; Q60; Q61; Q62; Q63; Q64; Q65; Q66; Q67; Q68; Q69; Q70; Q71; Q72; Total QOL; Depression Total; Flushing Total; Respiratory Total; Gastrointestinal Total; Cardiovascular Total; Physical Functioning Total; Positive Attitude Total; Pancreastatin Norm.; Pancreastatin Normal?; NKA; NKA Normal?; Serotonin Norm.; Serotonin Normal?; 5-HIAA; 5-HIAA; CGA Norm.; CGA Normal?; Gastrin; and Gastrin Normal?.

   There is a second spreadsheet of data that contain the biomarker specific data by themselves, and the data fields are specified as follows: Patient ID; Date; Primary Site; Pancreastatin; Pancr Normal range; Pancreastatin Norm.; Date Pancr.; NKA ; Date NKA; Serotonin; Serotonin normal range; Serotonin Norm.; Date Serot.; 5-HIAA; Date 5-HIAA; CGA; CGA normal range; CGA Norm.; Date CGA; Gastrin; Gastrin normal range; and Date Gastrin. The biomarker data are the same as the variables in the first spreadsheet.

4. Responsibilities of Data Recipient. Data Recipient agrees to:

    a. Use or disclose the LDS only as permitted by this Agreement or as required by law;

    b. Use appropriate safeguards to prevent use or disclosure of the LDS other than as permitted by this Agreement or required by law;

    c. Report to Data Provider any use or disclosure of the LDS of which it becomes aware that is not permitted by this Agreement or required by law;

    d. Require any of its subcontractors or agents that receive or have access to the LDS to agree to the same restrictions and conditions on the use and/or disclosure of the LDS that apply to Data Recipient under this Agreement; and

    e. Not use the information in the LDS to identify or contact the individuals who are data subjects.

5. Permitted Uses and Disclosures of the LDS. Data Recipient may use and/or disclose the LDS **for its Research activities only.**

6. Term and Termination.

    a. Term. The term of this Agreement shall commence as of the Effective Date and shall continue for so long as Data Recipient retains the LDS, unless sooner terminated as set forth in this Agreement.

    b. Termination by Data Recipient. Data Recipient may terminate this agreement at any time by notifying the Data Provider and returning or destroying the LDS.

    c. Termination by Data Provider. Data Provider may terminate this agreement at any time by providing thirty (30) days prior written notice to Data Recipient.

    d. For Breach. Data Provider shall provide written notice to Data Recipient within ten (10) days of any determination that Data Recipient has breached a material term of this Agreement. Data Provider shall afford Data Recipient an opportunity to cure said alleged material breach upon mutually agreeable terms. Failure to agree on mutually agreeable terms for cure within thirty (30) days shall be grounds for the immediate termination of this Agreement by Data Provider.

    e. Effect of Termination. Sections 1, 4, 5, 6(e) and 7 of this Agreement shall survive any termination of this Agreement under subsections c or d.

7. Miscellaneous.

a. Change in Law. The parties agree to negotiate in good faith to amend this Agreement to comport with changes in federal law that materially alter either or both parties' obligations under this Agreement. Provided however, that if the parties are unable to agree to mutually acceptable amendment(s) by the compliance date of the change in applicable law or regulations, either Party may terminate this Agreement as provided in section 6.

b. Construction of Terms. The terms of this Agreement shall be construed to give effect to applicable federal interpretative guidance regarding the HIPAA Regulations.

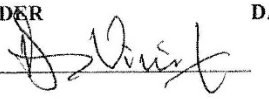
c. No Third Party Beneficiaries. Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

d. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

e. Headings. The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement.

IN WITNESS WHEREOF, each of the undersigned has caused this Agreement to be duly executed in its name and on its behalf.

DATA PROVIDER

Signed: 

Print Name: Dr. Aaron Vinik
Print Title: Professor, EVMS Neuroendocrine Unit

DATA RECIPIENT

Signed: 

Print Name: Stephanie Ford-Scheimer
Print Title: PhD Student

Appendix B: Norfolk QOL-NET Instrument

Gmail by Google

Stephanie Ford-Scheimer <sfordscheimer@gmail.com>

FW: NORFOLK QOL-NET

Vinik, Etta J. <vinikej@evms.edu> Tue, Dec 1, 2015 at 12:02 PM
To: Stephanie Ford-Scheimer <sfordscheimer@gmail.com>
Cc: "Vinik, Aaron I." <vinikai@evms.edu>

Dear Stephanie,

I confirm that you have permission to include a copy of the Norfolk QOL-NET in the appendices of your dissertation.

Best regards,

Etta Vinik, MA(Ed)

From: Stephanie Ford-Scheimer [mailto:sfordscheimer@gmail.com]
Sent: Tuesday, December 01, 2015 10:33 AM
To: Vinik, Etta J.
Subject: Re: FW: NORFOLK QOL-NET

[Quoted text hidden]

Quality of Life Questionnaire
Neuroendocrine Version

Name: _____ **Date:** _____

Subject #: _____ **Visit:** _____

Date of Birth: _____ **Gender:** ❑ Male ❑ Female

Race: ❑ White ❑ Black ❑ Hispanic
❑ Native American[1] ❑ Asian / Pacific Area[2]
❑ Other: _____

[1] Native American includes American Indian, Eskimo, and Aleut
[2] Pacific Area Embraces Polynesian (including Hawaiian and Samoan), Micronesian (including Guamanian), and Melanesian

Have you ever been told that you have or had a carcinoid tumor? ❑ Yes ❑ No

Do you have a family history of neuroendocrine tumors? (Bowel, pancreas, pituitary, parathyroid, thyroid, adrenal, medullary carcinoma of the thyroid, carcinoid, pheochromatocytoma, pulmonary bronchi) ❑ Yes ❑ No

Do you have an endocrine tumor? (Bowel, pancreas, pituitary, parathyroid, thyroid, adrenal, medullary carcinoma of the thyroid, carcinoid, pheochromatocytoma, pulmonary bronchi) ❑ Yes ❑ No

In the past month, have you lost weight without trying? ❑ Yes ❑ No

If yes, how much weight have you lost? _____ pounds

Do you have a history of high blood pressure? ❑ Yes ❑ No

Do you have any carcinoid or NET-related symptoms? (Flushing, diarrhea, rash, etc.)
❑ Yes ❑ No

How long have you had any carcinoid or NET-related symptoms that interfered with your daily life?
_____ Years _____ Months

How long before you were diagnosed with carcinoid tumor? _____ Years _____Months

Do you have flushing? (Redness and/or feeling of warmth in face, neck, or upper body)
❑ Yes ❑ No

If so, is the flushing hot? ❑ Yes ❑ No

Do you sweat when you flush? ❑ Yes ❑ No

How long does flush last? _____

Part Ia: Symptom Frequency

In the past 4 weeks, **how often** have you had any of the following symptoms? Please check the appropriate boxes with "X."	No Symptoms	Less than once a month	Less than once a week	Less than once a day	More than once a day
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
1. Flushing	❑	❑	❑	❑	❑
2. Joint/bone pain	❑	❑	❑	❑	❑
3. Other pain	❑	❑	❑	❑	❑
4. Swelling of hands and feet (Peripheral edema)	❑	❑	❑	❑	❑
5. Making a whistling sound when you breathe (Wheezing)	❑	❑	❑	❑	❑
6. Diarrhea or Constipation	❑	❑	❑	❑	❑
7. Rash	❑	❑	❑	❑	❑
8. Blueness of skin (Cyanosis)	❑	❑	❑	❑	❑
9. Red spots on skin (Telangiectasia)	❑	❑	❑	❑	❑
10. Fatigue	❑	❑	❑	❑	❑
11. Coughing	❑	❑	❑	❑	❑

Part Ib: Symptom Severity

In the past 4 weeks, **how severe** were any of the following symptoms? Please check the appropriate boxes with "X."	No Symptoms	Mildly severe	Moderately severe	Severe	Extremely severe
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
12. Flushing	❑	❑	❑	❑	❑
13. Joint/bone pain	❑	❑	❑	❑	❑
14. Other pain	❑	❑	❑	❑	❑
15. Swelling of hands and feet (Peripheral edema)	❑	❑	❑	❑	❑
16. Making a whistling sound when you breathe (Wheezing)	❑	❑	❑	❑	❑
17. Diarrhea or Constipation	❑	❑	❑	❑	❑
18. Rash	❑	❑	❑	❑	❑
19. Blueness of skin (Cyanosis)	❑	❑	❑	❑	❑
20. Red spots on skin (Telangiectasia)	❑	❑	❑	❑	❑
21. Fatigue	❑	❑	❑	❑	❑
22. Coughing	❑	❑	❑	❑	❑

Part II: Activities of Daily Life

Please check the appropriate boxes with "X."	Not a problem	Very mild problem	Mild problem	Moderate problem	Severe problem
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
23. In the past 4 weeks, have any of your symptoms kept you awake or woken you at night?	❑	❑	❑	❑	❑
24. In the past 4 weeks, have had diarrhea (even if you did not eat)?	❑	❑	❑	❑	❑
25. In the past 4 weeks, have you had continuous diarrhea (even if you did not eat)?	❑	❑	❑	❑	❑
26. In the past 4 weeks, have you had a cough (not related to a cold or allergies)?	❑	❑	❑	❑	❑
27. In the past 4 weeks, has wheezing bothered you?	❑	❑	❑	❑	❑
28. In the past 4 weeks, has shortness of breath with or without activity bothered you?	❑	❑	❑	❑	❑
29. In the past 4 weeks, have you noticed shortness of breath when lying flat?	❑	❑	❑	❑	❑
30. In the past 4 weeks, did you notice any skin color changes?	❑	❑	❑	❑	❑
31. In the past 4 weeks, did you have any abdominal pain or spasms?	❑	❑	❑	❑	❑
32. In the past 4 weeks, were you able to get out of a chair without pushing on the arms or seat of it?	❑	❑	❑	❑	❑
33. In the past 4 weeks, were you able to do your own hair?	❑	❑	❑	❑	❑
34. In the past 4 weeks, have you noticed swelling of your ankles?	❑	❑	❑	❑	❑
35. In the past 4 weeks, has your flushing (redness/warmth of your face) been affected by any of the following: the size of your meals, alcohol consumption, tomatoes, fatty foods, beverages with caffeine, chocolate, or spicy foods?	❑	❑	❑	❑	❑
36. In the past 4 weeks, has flushing (redness/warmth of face) bothered you?	❑	❑	❑	❑	❑
37. In the past 4 weeks, has there been a change in your appetite?	❑	❑	❑	❑	❑
38. In the past 4 weeks, have you become increasingly tired over the course of the day?	❑	❑	❑	❑	❑
39. In the past 4 weeks, how would you describe your energy level for regular work or other activities of daily living?	❑	❑	❑	❑	❑

Part II: Activities of Daily Life

In the past 4 weeks, **how much difficulty** have you had performing the following activities?	Not a problem	Very mild problem	Mild problem	Moderate problem	Severe problem
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
40. Bathing/Showering?	❑	❑	❑	❑	❑
41. Dressing?	❑	❑	❑	❑	❑
42. Walking?	❑	❑	❑	❑	❑

In the past 4 weeks, how much has your physical or emotional health interfered with your work or other regular daily activities?	Not at all	Rarely	Somewhat	Moderately	Severely
Answer these questions according to the following scale:	**0**	**1**	**2**	**3**	**4**
43. Cut down on the amount of time you spent on work or other activities?	❑	❑	❑	❑	❑
44. Accomplished less than you would like?	❑	❑	❑	❑	❑
45. Were limited in the kind of work or other activities you could perform?	❑	❑	❑	❑	❑
46. Had difficulty performing the work/other activities (it took extra effort)?	❑	❑	❑	❑	❑
47. In the past 4 weeks, to what extent has your physical health interfered with your normal social activities with family, friends, neighbors, or groups?	❑	❑	❑	❑	❑
48. In the past 4 weeks, how much did **pain** interfere with your normal work (including work both outside the home and housework)?	❑	❑	❑	❑	❑
49. In the past 4 weeks, how much did **other symptoms** interfere with your normal work (including work both outside the home and housework)?	❑	❑	❑	❑	❑

50. In general, would you say your health now is:

Excellent	Very Good	Good	Fair	Poor
❑	❑	❑	❑	❑

51. Compared with 3 months ago, how would you rate your health in general now?

Much Better	Somewhat Better	About the Same	Somewhat Worse	Much Worse
❑	❑	❑	❑	❑

52. In the past 4 weeks, how would you describe your energy level for regular work or other activities of daily living?

Excellent	Very Good	Good	Fair	Poor
❑	❑	❑	❑	❑

53. In the past 4 weeks, how would you describe your energy level for exercise?

Excellent	Very Good	Good	Fair	Poor
❑	❑	❑	❑	❑

54. How often do you need to use rescue meds (sandostatin, SAR boluses, or injections)?

Not at all	Every six months	Every three months	Every month	Every week	Every day
❑	❑	❑	❑	❑	❑

Part III: Somatostatin Injection Scale

Please select which best describes how you feel about your sandostatin injections. **Answer these questions according to the following scale:**	Never **0**	Rarely **1**	Sometimes **2**	Often **3**	Very often **4**
55. When you are given your injections (or when you give the injection yourself), do you feel scared, tense, nervous, fidgety, or sweaty?	❑	❑	❑	❑	❑
56. When you are given your injections (or when you give the injection yourself), do you feel your heart beat faster or begin to shake?	❑	❑	❑	❑	❑
57. When you are given your injections (or when you give the injection yourself), do you have difficulty breathing?	❑	❑	❑	❑	❑
58. When you are given your injections (or when you give the injection yourself), does your stomach feel upset?	❑	❑	❑	❑	❑

Part IV: Feelings Scale

Please select which best describes how often you felt or behaved this way ***OVER THE PAST 7 DAYS***.

Answer these questions according to the following scale:	Never **0**	Rarely (less than 1 day) **1**	Little or some of the time (1-2 days) **2**	Occasionally or a moderate amount of time (3-4 days) **3**	Most or all of the time (5-7days) **4**
59. Have you been bothered by things that usually did not bother you?	❑	❑	❑	❑	❑
60. Have you been overeating or under eating?	❑	❑	❑	❑	❑
61. Have you felt that you could not shake off the blues, even with help from your family and friends?	❑	❑	❑	❑	❑
62. Have you had trouble keeping your mind on what you were doing?	❑	❑	❑	❑	❑
63. Have you felt sad, depressed, or had crying spells?	❑	❑	❑	❑	❑
64. Have you had trouble falling asleep or staying asleep (insomnia)?	❑	❑	❑	❑	❑
65. Have you felt "lonely" when there were other people around?	❑	❑	❑	❑	❑
66. Have you had difficulty getting up and "going" in the morning?	❑	❑	❑	❑	❑
67. Have you felt hopeful about the future?	❑	❑	❑	❑	❑
68. Have you enjoyed life?	❑	❑	❑	❑	❑
69. Have you been satisfied with how you're coping with your illness?	❑	❑	❑	❑	❑
70. Have you worried about your illness?	❑	❑	❑	❑	❑
71. Have you worried about dying?	❑	❑	❑	❑	❑
72. Have you been easily annoyed?	❑	❑	❑	❑	❑