Spring 5-2018

Uncertainty in Illness and Health Literacy in Pancreatic Cancer Patients

Rae Reynolds

UNCERTAINTY IN ILLNESS AND HEALTH LITERACY IN PANCREATIC CANCER PATIENTS

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON

CIZIK SCHOOL OF NURSING

BY

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MAY 2018

Approval Form D-3

The University of Texas Health Science Center at Houston
School of Nursing
Houston, Texas

2/28/18
Date

To the Dean for the School of Nursing:

I am submitting a dissertation written by Rae Brana Reynolds and entitled "Uncertainty and Health Literacy in Pancreatic Cancer Patients". I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.

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Acknowledgements

I thank the American Cancer Society (ACS) for awarding me the ACS Doctoral Research Scholarship in Nursing. The generous sponsorship from the ACS facilitated fulfillment of this degree.

I have deep gratitude for the members of my dissertation committee. Thank you to my Committee Chair, Dr. Geri Wood, who encouraged and challenged me to develop in scholarship and research. Dr. Wood fostered growth and achievement with expert advice, kind support, and constructive feedback. I have great appreciation for Dr. Terri Armstrong who listened to big, hopeful ideas and provided guidance in shaping them into an organized structure for research. I am grateful for Dr. Armstrong's continued tutelage and commitment to seeing me complete this process even after her transition to the NIH. I am grateful to Dr. Nikhil Padhye whose instruction was invaluable from the first PhD semester to the last. Dr. Padhye's calm counsel and patience was instrumental in completing this project. I thank Dr. Matthew Katz for sharing his knowledge, expertise, and resources. Dr. Katz' enthusiasm and generosity buoyed my excitement in pancreatic cancer care and research.

I will always be thankful to my Department Chair, Dr. Jeffrey E. Lee, who has allowed me opportunities to pursue career and academic advancement. I am grateful to Dr. Lee for sharing his patients with me over the years and for helping cultivate my interest in caring for cancer patients.

I will recall with enduring fondness the friendships made and deepened during my time in the PhD program. I acknowledge the encouragement, advice, and technical assistance from newfound friends Dr. Seema Aggarwal, Dr. Nate Parker and Vanessa

Martinez as well as the support of long-time friends Alison Mitchell, JoAnn Rodriguez, Josie Arungayan, Joy Panes, Maggie Villasin and Paz Tiongson.

I am immensely grateful for my family. I thank my parents, Rollen and Alma Brana, who consistently encourage growth not only in knowledge but more importantly, in kindness and wisdom. I thank my brother, Kiril Brana, and sister, Shehanie Brana, for their inspiring sense of adventure. I thank my nephews, Chris Brana, Sam Brana, and Steve Brana, who promote a sense of wonder and discovery. I especially thank my husband, Jeff Reynolds, for his loving prayers and unwavering support.

I thank God for allowing me amazing opportunities, challenges, and blessings. I am grateful for the people He has allowed in my life. His mercies are new every day and His faithfulness endures forever.

Rae Brana Reynolds

Uncertainty in Illness and Uncertainty in Pancreatic Cancer Patients

May 2018

Abstract

Background: Despite a shared link to cognitive processing of health information suggested by their definitions, information on the association between uncertainty and health literacy is scarce. Their relationship has not been studied in pancreatic cancer patients.

Aims: To evaluate uncertainty and health literacy in pancreatic cancer patients, examine their bivariate correlation, and determine significant predictors.

Methods: This descriptive, cross-sectional study was conducted in a comprehensive cancer center. Uncertainty was measured using the Mishel Uncertainty in Illness Scale - Community and health literacy was measured using the Cancer Health Literacy Test 30. Spearman's rho tested correlation and linear regression models were used to test for predictors. Bias corrected, accelerated bootstrap was used when regression residuals violated normality.

Results: The sample (N=82) was predominantly male (55%), White/Caucasian (79%), married 74%), and receiving neo-adjuvant treatment in anticipation of potential surgical resection (49%). Mean age was 64.59 years ranging from 30 to 80. A significant but weak correlation was noted between uncertainty and health literacy (r_s = -.24, p = .032). Health literacy was not a significant predictor of uncertainty after adjusting for age, gender, education, race/ethnicity, and phase of care. Education was a significant predictor of uncertainty (p = .001; η_p^2 = .217) and health literacy (p =.003; η_p^2 = .174). Phase of care was a significant predictor of uncertainty (p = .001; η_p^2 = .221).

Conclusion: Health literacy and uncertainty had a significant albeit weak correlation. Health literacy is multifaceted and some of its features were accounted for by other socioeconomic and clinical variables. Education was a significant predictor of uncertainty and health literacy. Significant differences in the ability to interpret health events were found through the different phases of the pancreatic cancer experience. Sample homogeneity restricted inferences and generalizability on effects of race/ethnicity.

Keywords: *uncertainty, health literacy, pancreatic cancer*

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PUBLICATIONS

A. **Brana Reynolds. R,** & Folloder, J.P. (2014). Clinical management of pancreatic cancer. *Journal of the Advanced Practitioner in Oncology*, 5(5)356-364. 171

B. **Brana Reynolds, R**., & Folloder, J.P. (2014). Translating research into practice: Use of radiographic criteria to predict outcomes after surgery for pancreatic cancer. *Journal of the Advanced Practitioner in Oncology*, 5(5), 365-370 …… 180

C. **Reynolds, R.B.,** McCoy K. (2016). The role of Advanced Practice Providers in interdisciplinary oncology care in the United States. *Chinese Clinical Oncology*, 5(3):44. doi: 10.21037/cco.2016.05.01 …… 186

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Summary of the Study

The research protocol "Uncertainty in Illness and Uncertainty in Pancreatic Cancer Patients" was executed following approval from the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center on May 10, 2017 and from the Committee for the Protection of Human Subjects (CPHS) of The University of Texas Health Science Center at Houston on June 5, 2017. The aims of this descriptive, cross-sectional research study were to:

1. Describe uncertainty using the Mishel Uncertainty in Illness Scale – Community instrument (MUIS-C) and health literacy using the Cancer Health Literacy Test – 30 (CHLT-30) in the pancreatic cancer population
2. Examine the association between uncertainty and health literacy in the pancreatic cancer patient population
3. Examine if health literacy is a significant predictor of uncertainty after adjusting for age, gender, race and ethnicity, education level, and disease treatment stage

Data collection began on June 9, 2017 and concluded on December 22, 2017. Study instruments were administered to participants with pancreatic adenocarcinoma recruited in the outpatient clinics at MD Anderson Cancer Center. Following application of inclusion, exclusion, and sample selection criteria 91 participants were registered and the final sample comprised of 82 evaluable pancreatic cancer patients.

Two study protocol amendments were submitted and approved by the Institutional Review Board. The first approved amendment clarified that patients with pancreatic adenocarcinoma who have either received oncologic treatment for another primary malignancy or have active disease from another primary malignancy within the past 5

years were ineligible for the study unless the other primary malignancy was a non-melanoma skin cancer. The second approved amendment clarified that participants complete the MUIS-C before their meeting with the physician. Study procedure already adhered to this but it was specified with a formal amendment.

Descriptive statistics were employed to describe uncertainty and health literacy. Spearman's rho tested correlation and linear regression models tested for significant predictors. Bias corrected, accelerated bootstrap was utilized when regression residuals violated normality. The findings revealed a significant albeit weak correlation between uncertainty and health literacy. Education level was a significant predictor of uncertainty and health literacy. Significant differences in uncertainty levels were found through the different phases of the pancreatic cancer experience. Sample homogeneity restricted inferences and generalizability on effects of race/ethnicity.

A manuscript was written describing the background and significance of the research questions along with methods, results, and implications for future research. Appendices A-I contain supplemental information from the study including the IRB and CPHS approval documents, MDACC protocol and IRB-approved amendments, study consent form, study instruments, and human subjects research training certificates.

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Specific Aims

Uncertainty during the cancer illness experience is associated with poor health outcomes (Lin et al., 2015). Although uncertainty has been studied in patients with breast cancer, prostate cancer, brain tumors, renal malignancies, gynecologic malignancies, and lymphoma (Bailey et al., 2011; Cahill et al., 2014; Elphee, 2008; Germino et al., 2013; McCorkle et al., 2009; Mishel et al., 2002; Mishel et al., 2009; Parker et al., 2013), it has not been explored with a focus on pancreatic cancer patients. Many of these studies show that uncertainty interventions aimed at enhancing knowledge about diagnosis, management and surveillance as well as communication skills are effective. However, assessment of uncertainty in the pancreatic cancer population is necessary prior to effective implementation of interventions.

Pancreatic cancer has unique characteristics that warrant baseline studies prior to implementing interventions found effective in other populations. The pancreatic cancer experience is fraught with ambiguity, complexity, and unpredictability due to an aggressive and recalcitrant biology, lack of prevention guidelines and screening standards for the general population, and lack of expert conformity on the sequence of treatment for patients with resectable disease (Halperin & Varadhachary, 2014; Reynolds & Folloder, 2014). These attributes of pancreatic cancer predispose patients to an illness experience beset with uncertainty.

Uncertainty is defined as the inability to determine the meaning of *illness*-related events and it is conceptualized as having associated antecedents and consequences (Mishel, 1988). Antecedents and predisposing factors that can potentially influence uncertainty are important to explore. One factor to examine is health literacy, defined as

the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Dumenci et al., 2014). Health literacy has emerged essential in health promotion studies and has been found influential in cancer health outcomes (Altsitsiadis et al., 2012; Busch, Martin, DeWalt, & Sandler, 2015; Halverson et al., 2015; Husson, Mols, Fransen, van de Poll-Franse, & Ezendam, 2015). However, it has not been studied with a focus on pancreatic cancer patients. In fact, the association between health literacy and uncertainty has yet to be explored in the cancer population and there is a dearth of general information on the association between these variables despite a shared connection to cognitive processing of health information described in their respective definitions. Evaluating this association is valuable to understanding the relevance and applicability of both in improving the care of pancreatic cancer patients. The aims of the study are:

1. Describe uncertainty in the pancreatic cancer patient population using the Mishel Uncertainty in Illness Scale – Community instrument (MUIS-C)
2. Describe health literacy using the Cancer Health Literacy Test – 30 (CHLT-30) and its association to uncertainty in the pancreatic cancer patient population

   Hypothesis 2a: Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients

   Hypothesis 2b: Health literacy is an independent predictor of uncertainty in pancreatic cancer patients
3. Examine if age, gender, race/ethnicity, education status, and phase of care are significant predictors of uncertainty and health literacy in the pancreatic cancer population

Hypothesis 3a: Education status, race/ethnicity, and phase of care are significant predictors of uncertainty and of health literacy in pancreatic cancer patients

Hypothesis 3b: Age and gender are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients

Pancreatic cancer has distinct characteristics that predispose patients to uncertainty. Successful understanding and navigation of the complexities of disease and treatment that can mitigate uncertainty require proficient health literacy. Given the cognitive processing of health information described in their respective definitions, exploring the association between uncertainty and health literacy has merit and beneficial implications for clinical practice and research. This study will explore uncertainty and health literacy as distinct phenomena in the pancreatic cancer population and examine the relationship between the two variables. This study will fill significant research gaps with information that can improve clinical interventions, research and patient outcomes.

Background and Significance

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States (American Cancer Society [ACS], 2016). It has no established screening or prevention guidelines, no hallmark symptoms to help distinguish disease at an early stage and 80% of pancreatic cancer patients present with metastatic and locally advanced disease at initial diagnosis (Chatterjee et al., 2012). This leaves a minority of patients eligible for curative treatment. For patients undergoing treatment, there is debate among experts regarding the sequence of therapy for patients with resectable disease (Brana Reynolds & Folloder, 2014; Evans et al., 2008; Varadhachary et al., 2008). The National Comprehensive Cancer Network (NCCI) recommends upfront surgery for potentially-

resectable disease but expert consensus and a number of phase II clinical trials support administration of neoadjuvant chemotherapy in selected patients with biopsy-proven carcinoma prior to surgery (Halperin & Varadhachary, 2014). Even for patients who complete treatment, the widely-acknowledged high recurrence rate undermines confidence in having achieved long-term survival or cure. The 5-year survival rate for pancreatic cancer remains low at 6% (ACS, 2016) and approximately 80% of patients undergoing resection with curative intent develop distant metastasis or local recurrence within five years of surgery (Halperin & Varadhachary, 2014). With a grim prognosis, patients may become overly vigilant and mistakenly interpret symptoms unrelated to malignancy as indications of disease recurrence. These factors contribute to uncertainty throughout the patient's illness experience from initial presentation to survivorship and end-of life.

Uncertainty in Illness (Figure 1), is the inability to determine meaning of illness-related events (Mishel, 1988). It is a cognitive state that occurs when lack of adequate knowledge leads to the inability to frame or categorize an event. Studies on uncertainty in multiple cancer populations have utilized Mishel's theoretical framework and have suggested that uncertainty influences psychosocial adaptation and can affect disease outcomes (Lin et al., 2015). Patients with cancer have also been found to benefit from interventions aimed at addressing uncertainty during their illness (Mishel et al., 2009). Studies on uncertainty have been conducted on patients with breast cancer (Germino et al., 2013; Gil et al., 2006), prostate cancer (D. E. Bailey, Jr. et al., 2011; D. E. Bailey, Mishel, Belyea, Stewart, & Mohler, 2004; Kazer, Psutka, Latini, & Bailey, 2013; Mishel et al., 2002; Mishel et al., 2009; Wallace, 2005), gynecological malignancies (McCorkle

et al., 2009), renal malignancies (Parker et al., 2013), lymphoma (Elphee, 2008), and brain cancer (Cahill, Gilbert, & Armstrong, 2014; Cahill, Lin, et al., 2014; Lin et al., 2015). However, there is a research gap in examining uncertainty in the pancreatic cancer experience and this gap requires research aimed at discovering baseline information so that the uncertainty experienced by pancreatic cancer patients is evaluated before testing and implementing interventions that have been found effective in other cancer populations.

Although uncertainty has been explored in patients with other aggressive malignancies, there are unique aspects to pancreatic cancer that warrant investigation focused on this population. The lack of conformity of treatment sequence for curable disease can cause confusion among newly diagnosed patients seeking information and guidance in making treatment decisions. Conflicting information from clinicians on whether one should pursue upfront surgery versus neo-adjuvant therapy can present complex challenges that potentiate uncertainty and require a high level of health literacy to parse through. There are other distinct aspects in the pancreatic cancer population such as its widely-acknowledged high recurrence rate. A recent study that examined fear of recurrence in 240 patients with pancreatic and peri-ampullary tumors included 94 patients with pancreatic adenocarcinoma who had completed treatment with curative intent and found that 37% of these patients reported frequent fearful thoughts, emotional disturbance and functional impairment (Petzel et al., 2012). This concern over the unpredictability of disease merits investigation. In a disease with vague but distressing symptoms, aggressive and recalcitrant biology, and complex treatments, it is necessary to assess precursors and associated factors to identify ways to mitigate uncertainty.

Uncertainty is conceptualized by Mishel's Uncertainty in Illness Theory (Figure1) as having antecedents namely the *stimuli frame*, the patient's *cognitive capacity*, and *structure providers* that include patient education, social support, and credible authority (Mishel, 1988). Stimuli frame is the composition and structure of the stimuli in illness and treatment-related events and include event unfamiliarity, a lack of symptom pattern, and lack of event congruence (Mishel & Braden, 1988). Structure providers are information and support sources that help patients interpret variables in the stimuli frame. Structure providers include credible authorities, education, and social support (Mishel, 1988). Cognitive capacity refers to the information-processing abilities that enable patients to make sense of their experience (Mishel et al., 2009). The theory posits that an inability to form a cognitive structure allowing for interpretation of illness-related events can lead to uncertainty.

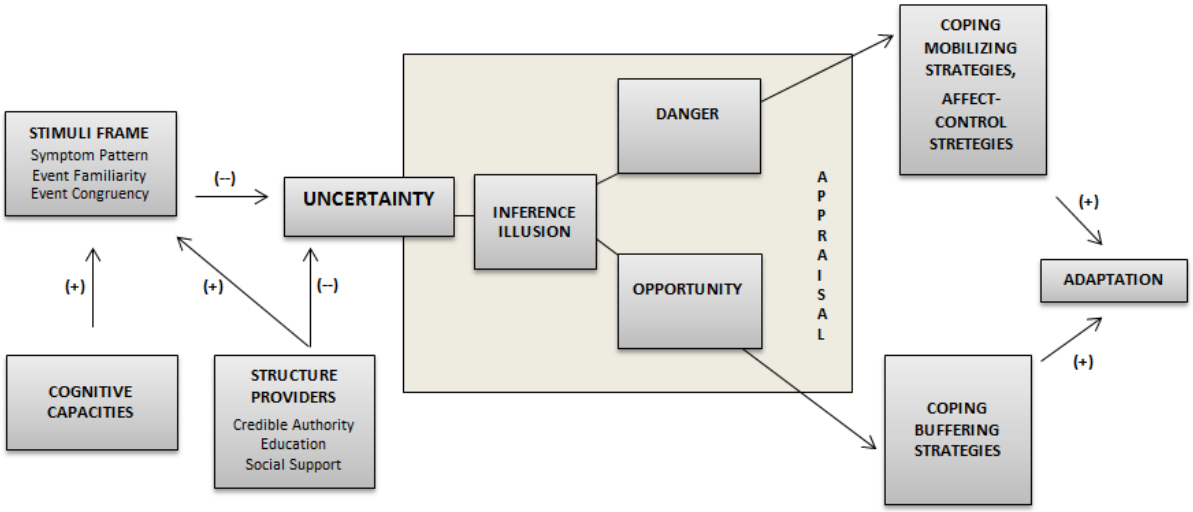

Figure 1. Uncertainty in Illness (Mishel, 1988)

One factor not explicitly addressed in the theoretical framework is health literacy, defined by the Institute of Medicine and by the US Department of Health and Human Services as the degree to which individuals have the capacity to obtain, process, and

understand basic health information and services needed to make appropriate health decisions (Cutilli & Bennett, 2009; Dumenci et al., 2014). Concept analyses have ascribed reading and numeracy skills, comprehension, capacity to use information in health care decision-making, and successful functioning as a health care consumer as defining attributes of health literacy (Mancuso, 2008; Speros, 2005). Mancuso (2008) classifies the attributes in three categories with the first being *capacity* which involves the verbal, numerical, and social skills essential to advocating for oneself while negotiating the health care system. The second is *comprehension which involves the in*teraction of logic, language, and experience essential to interpretation of information. The third is c*ommunication* which involves intake, processing, output, and feedback of messages through speech, writing, or behavior. In addition to having these attributes, health literacy has been described as having three classes (Nutbeam, 2000). *Functional literacy* involves reading and writing skills for everyday situations while *interactive literacy* involves advanced cognitive skills combined with social skills that allows a person to extract information, derive meaning from different forms of communication and apply such to changing circumstances (Nutbeam, 2000). *Critical literacy* involves cognitive skills combined with social skills applied to critically analyze information and utilize such to exert greater control over life events (Nutbeam, 2000; Chinn, 2011).

The definition and conceptualization of health literacy suggest a link to uncertainty but thee variables have not been studied in association with each other in cancer patients. In fact, there is a dearth of information on the relationship between these variables in general. Literature search with the terms “uncertainty” and “health literacy” using the Cumulative Index of Nursing and Allied Health Literature (CINAHL)

generated only one report out of 12 results that actually studied the association between the two variables and it was not in the cancer population. The report is an abstract by Mock (2013) describing a pilot study to examine the correlation between health literacy and uncertainty during acute hospitalization in 25 older adults with heart failure. The abstract reported health literacy to be significantly correlated to uncertainty (Mock, 2013). A search using Pubmed generated no research reports examining the association between these variables. One article discussed health literacy in advance care planning in the context of proposing a theoretical model on *Uncertainty in advance care planning for African Americans* (Melhadho and Bushy, 2011). The theory posits that improving health literacy skills and addressing domains of the uncertainty in advance care planning can promote end-of life discussions decision-making (Melhadho and Bushy, 2011). The absence of prior research on the uncertainty of pancreatic cancer patients, the scarcity of information on the relationship of uncertainty and health literacy, and the lack of information on health literacy in the pancreatic cancer population underscores the significance of this study.

Health literacy has evolved into an essential component in efforts to improve health outcomes and is included in *Healthy People 2020* as an objective in the promotion of health communication (Office of Disease Prevention and Health Promotion; 2016). According to the US Department of Education, only 12% of English-speaking adults have proficient health literacy skills (Hepburn, 2012, US Department of Health and Human Services, 2010). If this pattern holds true in the pancreatic cancer population, this is a detriment to care access and delivery as patients in this population are often required to navigate their way through information systems and interact with health care providers

in order to understand their illness, access appropriate services and participate effectively in health care decision making.

Health literacy has become more critical as patients try to navigate the ever-evolving health care environment and traverse information pathways. The promulgation of web-based medical information, shifts in health policy and system access, as well as advances in cancer management make health literacy essential to successful navigation of the health care system. Exploring health literacy is especially significant in populations such as pancreatic cancer patients where treatment decisions can be complex.

There is a growing body of evidence suggesting that limited health literacy negatively affects cancer prevention and disease management behaviors. Studies in patients with colon cancer (Pendlimari, Holubar, Hassinger, & Cima, 2012), breast cancer (Buki, Yee, Weiterschan, & Lehardy, 2015; Halbach et al., 2015; Kamimura et al., 2016), cervical cancer (Sentell, Braun, Davis, & Davis, 2015), prostate cancer (Kayser, Hansen-Nord, Osborne, Tjonneland, & Hansen, 2015), lung cancer (Milne et al., 2015), and head and neck cancer (Koay et al., 2013) have explored different aspects of health literacy and the impact of poor literacy on health outcomes in these patient populations. Preparation work for this proposal includes a search of Medline, Pubmed, CINAHL, and PsychINFO to review the body of research on health literacy and cancer health outcomes. Fifteen studies were found involving 11,326 patients with various cancers including melanoma, colorectal cancer, prostate cancer, breast cancer, and lung cancer. The health outcomes studied were quality of life (Husson, 2015; Song, 2012; Halverson, 2015; Milne, 2015), distress (Koay, 2013), decision satisfaction and regret over decision outcomes (Hawley, 2008), mental well-being (Song, 2012), medication adherence (Rust, 2011; Rust, 2012),

sunscreen and sunbed use (Altsitsiadis, 2012), receipt of treatment including chemotherapy, reconstructive surgery, salvage hormone therapy, genetic counseling (Mahal, 2015; Busch, 2015: Winton, 2016), disease status at diagnosis (Wolf, 2006), and survivorship (Hulett, 2015). The results of the quantitative studies primarily support low health literacy as having a negative association with health outcomes and the results of the qualitative studies suggest that patients perceive low health literacy as a barrier to good outcomes. The research gap in evaluating health literacy in the pancreatic cancer population needs to be addressed. Because health literacy may be a critical and modifiable factor in improving care and reducing health disparities, it is important to explore this in pancreatic cancer patients as well.

This planned study will be conducted within the context of a conceptual framework adapted from the Uncertainty in Illness Theory. The adaptation that will guide this planned study is depicted in Figure 2 and focuses on antecedents of uncertainty with incorporation of health literacy into the framework.

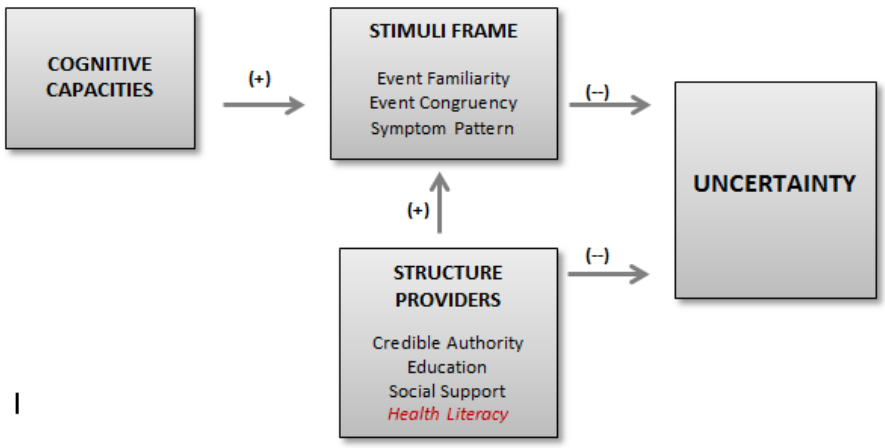

Figure 2. Antecedents to Uncertainty in Illness. Adapted from Uncertainty in Illness (Mishel, 1998)

The study will also examine demographic factors as potential determinants of uncertainty and health literacy to evaluate if there are demographic predictors that can guide future research and identification of individuals who are more susceptible to uncertainty. Prior health literacy assessment in 1,306 cancer patients found no significant mean difference between men and women ($p=.247$) but the scores among African Americans were found to be significantly lower ($p < .0001$) than White participants (Dumenci et al., 2014). This study found that participants with limited health literacy consisted of an overrepresentation of African-Americans, patients who were undereducated, and patients with lower income (Dumenci et al., 2014). Meanwhile aggregate data on different population subgroups described in the Uncertainty in Illness Scales Manual indicate no difference in the mean scores based on gender or age but that scores decrease with an increase in level of education (Mishel, 1997). These demographic variables will be evaluated as this can influence the design and implementation of future studies and intended population of intervention programs.

Innovation

Given the unique characteristics of pancreatic cancer, it is necessary to obtain baseline information before translating findings from other populations to patients with pancreatic cancer. This study will be innovative and significant to care delivery as it will explore important variables that have not been studied in this population. With the growing emphasis on health literacy, this study will explore health literacy as a structure provider antecedent to uncertainty within the context of the Uncertainty in Illness model. The innovation extends beyond theory testing and concept development as its practical implications can significantly improve patient outcomes, nursing interventions, and guide

future research efforts. The paucity of information on uncertainty and health literacy specific to the pancreatic cancer population is a barrier to improving health literacy and mitigating uncertainty. Results from this planned study can prove helpful in eventually allowing nurses and health care givers to influence the patient's ability to understand illness events and process health information and services that enhance their engagement in health decisions towards better outcomes.

Research Design and Methods

The study is designed as an observational, cross-sectional study seeking to describe uncertainty in illness and health literacy in the pancreatic cancer population and explore the relationship between variables. A cross-sectional design will be utilized to gather information during a single period of data collection with no repeat measures. Given the absence of prior studies on uncertainty and health literacy in pancreatic cancer patients, this design is appropriate as an initial exploration that can provide groundwork for future research.

Population, Sample, Sampling Procedure

The study population will be pancreatic cancer patients and the sample will be recruited from the pancreatic cancer clinics in the Gastrointestinal Center at The University of Texas MD Anderson Cancer Center. An estimated total of up to 91 patients will be invited to participate. With an anticipated response rate of approximately 90%, an analyzable sample size of 82 will be produced. The primary objective is to collect the uncertainty and health literacy information in pancreatic cancer patients and assess the correlation between uncertainty and health literacy. The primary endpoints are the Mishel uncertainty scores which is defined as the summation of all the questions scores

and the cancer health literacy test scores which is defined as the number of questions that the patient answers correctly. With 82 patients in total, given the two-sided type I error of 5%, we will have an 80% power to detect a Pearson's correlation of 0.3 between uncertainty score and cancer health literacy score. nQuery/nTerim version 3.0 was used for the sample size justification.

The pancreatic surgical clinic had over 1900 visits from patients who had ICD-10 diagnosis codes corresponding to pancreatic cancer in the year 2015. This number comprises a combination of patients who are newly diagnosed, under active treatment, and survivors who attend clinic ongoing five days a week. It is expected that accrual will be accomplished over a 6 month period. Consecutive sampling will be employed and patients will be recruited in the order of their visit and appointment dates.

Inclusion Criteria

1. Patients with a diagnosis of biopsy-proven pancreatic adenocarcinoma who are newly-diagnosed, receiving active treatment, receiving active oncologic surveillance or treatment follow-up, or receiving survivorship care
    a. Newly diagnosed – a patient who has biopsy confirmation of pancreatic adenocarcinoma but has not started treatment
    b. Active treatment – a patient who is currently receiving cancer therapy (chemotherapy, surgery, radiation) or treatment for complication of pancreatic adenocarcinoma
    c. Oncologic surveillance – a patient who is receiving treatment-related follow-up (post-op care, chemotherapy or radiation follow-up)

   d. Survivorship care – a patient who is 6 months or more from completion of treatment and has no evidence of recurrence or active disease

2. Patients who meet the above criteria and are 18 years of age or older

Exclusion Criteria

1. Patients who have a history or current diagnosis of another primary malignancy other than pancreatic adenocarcinoma
2. Patients unable to speak, read, or write in English will be excluded because the instruments are in English
3. Pancreatic adenocarcinoma patients who are under 18 years of age

Recruitment

Patients who meet the eligibility criteria will be invited to participate in the study when they present for a clinic visit. This will occur during a patient's scheduled visit to the clinic. Patients will not be required to report to clinic for the purpose of study participation on days when they otherwise do not have a scheduled visit for cancer treatment or follow-up. The voluntary nature of participation will be explained and informed consent will be obtained from patients who agree to take part in the study. The recruitment process will be as follows:

1. Primary investigator will review consecutive patients' medical records to determine eligibility
2. Primary investigator will approach the patient, explain the study and invite them to participate
3. The primary investigator will explain the Informed Consent process and voluntary nature of study participation

4. The primary investigator will address patient questions
5. The principal investigator will obtain signatures for Informed Consent
6. A copy of the completed consents will be kept in the electronic health record system

Patient Registration

Enrolled patients will be registered into the Clinical Oncology Research System (CORe) which serves as the MD Anderson Cancer Center institutional patient data management system.

Instruments

The Mishel Uncertainty in Illness Scale – Community Form (MUIS-C) will be used to measure uncertainty. The MUIS-C has 23 items scored 1 to 5 on a Likert scale. The item scores are summed with a higher cumulative score indicating greater uncertainty. The MUIS-C has been used extensively with cancer patients. The MUIS-C was adapted from the 33-item Mishel Uncertainty in Illness Scale (MUIS-A), originally developed to evaluate uncertainty in acutely ill, hospitalized adults (Bailey et al., 2011). Items from the MUIS-A specifically relating to inpatient hospitalization were removed and the remaining questions comprise the items for the MUIS-C version. The MUIS-A was developed through expert analysis and validation of the MUIS-A was utilized to support the validity of the MUIS-C (Bailey et al., 2011). In analyses of MUIS-C scores from 18 samples of chronically ill adults (total n=1068), Cronbach's alpha exceeded 0.85 in a large majority of the samples indicating the reliability of MUIS-C as comparable to the 0.87 reported for the MUIS-A (Bailey et al., 2011).

The Cancer Health Literacy Test – 30 (CHLT-30) (Dumenci, et. al., 2014) will be used to measure health literacy. The 30-item CHLT-30 was created to assess literacy along the cancer health literacy continuum. Its development was described in a publication of a study involving 1,306 adults with heterogenous cancer diagnoses, educational attainment, and health insurance and marital status. Pancreatic cancer was not listed as a category among the 11 diagnostic cancer types represented by the participants in the study sample. The reliability evidence for the CHLT-30 was a Cronbach's alpha of 0.88, McDonald's omega of 0.89, 2-week test–retest reliability of 0.90, and 6-month test–retest reliability of 0.90. There was support for the unidimensional scale and all variables had significant factor loadings of $\geq$ 0.44. Structural equation modeling supported external validity with self-confidence in engaging in health decisions specified as a latent variable measured by two positively and two negatively worded items. The test score is the total number of correct responses and ranges from 0 to 30. The instrument response time ranges from 10-15 minutes (Dumenci, et. al., 2014).

A Patient Demographic Form will be utilized to record demographic information including age, gender, education status, ethnicity, and marital status. The time to complete all instruments should not exceed 20 minutes.

Data Collection Procedures

Enrolled patients will complete the instruments in the clinic. Collaboration and coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment.

1. Data will be collected by paper and pencil surveys with the research staff entering information into the web-based REDCap application hosted by MD Anderson Cancer Center (https://redcap.mdanderson.org)
2. A member of the research staff will be available during the time the patient is completing the instruments
3. The research staff may not provide any answers to the specific questions on the questionnaire but can address questions about study participation or the process of form completion
4. Only the patient may complete the form. Family members or patient companions to the visit may not answer or complete the forms. If there are deficits that makes reading the questionnaire or writing the responses difficult, the questionnaire can be read to the patient by the research staff or the patient companion and the responses recorded according to the patient response
5. Research staff will review the forms to ensure completeness and will transport the completed forms to a secure location in the primary investigator's office

The time to complete the instruments should not exceed 20 minutes. The primary investigator or designated research staff will enter the data into a secure database. Data entry and instrument scoring will be conducted according to the instrument manuals and study protocol prepared for the study.

Data Analysis

Questionnaire scores will be calculated based on standardized manuals associated with each survey instrument. Descriptive statistics will be used to summarize scores of the questionnaires according to respective scoring manuals for

each of the measures. The distribution of each continuous variable will be summarized by its mean, standard deviation, median, and range. The distribution of each categorical variable will be summarized in terms of its frequencies and percentages. The difference in uncertainty and health literacy scores will be assessed between groups (e.g. gender, education levels) by a two-sample t-test or ANOVA if the data is normally distributed; otherwise a Wilcoxon rank sum or Kruskal-Wallis test will be used. The association between uncertainty scores and health literacy score will be examined by Pearson correlation. To identify factors associated with uncertainty or health literacy scores of the survey measures, for example, the patient education status, age, ethnicity, and gender, multivariate linear regression will be performed to examine their effects.

Specifically, the hypotheses testing and anticipated results are as follows:

1. Describe uncertainty in the pancreatic cancer patient population using the MUIS - this primary, exploratory aim will assessed using descriptive analysis
2. Describe health literacy using the CHLT-30 and its association to uncertainty in the pancreatic cancer patient population

   Hypothesis 2a: **Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients** - Pearson product moment correlation coefficient will be calculated. Kendall's tau b or Spearman rho will be used if there is not a linear relationship or normal distribution. The anticipated result will be an inverse linear association between uncertainty and health literacy.

Hypothesis 2b: **Health literacy is an independent significant predictor of uncertainty in pancreatic cancer patients** - Health literacy will be included in multivariate regression to evaluate if it is a significant predictor of uncertainty.

3. Examine significant demographic predictors of uncertainty and health literacy in the pancreatic cancer population

   Hypothesis 3a: Education status and ethnicity are significant predictors of uncertainty and of health literacy in pancreatic cancer patients – Multiple linear regression will be performed to determine if education status and ethnicity are significant predictors for uncertainty and multivariate regression will be also be performed assess if they are significant predictors for health literacy as well. The anticipated results will be that education status and ethnicity will be significant predictors for both health literacy and uncertainty.

   Hypothesis 3b: Age and gender are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients - Multivariate regression will be performed to determine if education status and ethnicity are significant predictors for uncertainty and multivariate regression will be also be performed assess if they are significant predictors for health literacy as well. The anticipated results will be that neither age not gender will come out as significant predictors for either uncertainty or health literacy.

Study Limitations

The lack of prior studies on uncertainty and health literacy focused on the pancreatic cancer population is a constraint as there is limited information to guide this investigation in this population. Sampling bias will be a concern as this sample will be

recruited from patients who have the ability to navigate the referral system and travel then to access care at a high-volume comprehensive cancer center. The participants will thus potentially represent patients who have higher income and better ability to traverse the health care system. As such, one would have to emphasize that the study results will have generalizability limitations to the general population of pancreatic cancer patients. Nonetheless, the information from this initial study on uncertainty and health literacy will provide valuable guidance for future studies. Patients who perceive their health literacy to be low may also be more apt to decline participation over concern of a stigma related to low health literacy.

Utilizing a cross-sectional design is deemed appropriate for this initial study on these concepts but it does not allow for repeated measures to assess for change in uncertainty levels as patients go through the phases of cancer treatment. A future study can be done as a longitudinal repeated measures design to examine a patient's the fluctuation or differences in uncertainty scores between the different phases of care after baseline information from this study has been obtained.

Strategies to Overcome Potential Problems

One concern to overcome is that patients may find it daunting to complete questionnaires during a time when they are stressed with emotional or physical challenges related to their illness. The investigator will take the time to explain the enrollment and study process to the patient, acknowledge the patient's valuable contribution, and elucidate the advances that can result from participation in the study. It is also important to prevent the perception that there is judgment of skills and capabilities so emphasis will be placed on the overarching goal of assessing the needs of pancreatic

cancer patients to help providers enhance their communication skills and improve the way they engage patients in health care decisions. The primary investigator will stress the importance for health providers to understand areas for improvement in their patient interactions in order to promote improved partnerships with their patients.

Human Subject Protection

Permission to conduct the study will be requested from the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center where the study will be conducted. Reciprocal permission will be requested from the Committee for the Protection of Human Subject of University of Texas-Houston following the guidelines of the university in partnership with MD Anderson Cancer Center.

Participants will be provided information on the potential risks, benefits, and the importance of knowledge gained from the study. The voluntary nature of the study will be emphasized and it will be explained to patients and clinicians that declination of participation in the study will not affect clinical treatment and/or care. The clinical team, case management or social work team assigned to the patient will be notified if the patient expresses questions or concerns about increased uncertainty about their care or raise questions about understanding of or access to resources.

The exclusion of patients who are non-English speaking is due to the lack of an instrument version translated for the assessment of health literacy in non-English speaking patients. As such, it would be unsuitable and detrimental to the validity of the study not to exclude them.

Confidentiality

To ensure confidentiality, paper forms of the completed instruments will be secured in a locked cabinet. All electronic files of questionnaires and the interviews will be kept on a password-protected secure server. Research staff who require access to electronic or paper files for analysis must relinquish access when analysis is not occurring. Files may only be accessed may not be kept by study personnel when not in use. Digital files are identified with participant study numbers only and not with names, medical record numbers, or other identifying information. When all analysis has been completed and all study results have been reported, the electronic and paper files will be stored securely in perpetuity.

Timeline

The study is expected to take 12 months from the time the proposal submission. The specific time points for each step of the study including dissertation writing and defense is outlined in Table 1 below.

Table 1

Study Timeline

	STUDY TIMELINE															
	2016				**2017**											
ACTIVITY	**FALL**				**SPRING**				**SUMMER**				**FALL**			
Proposal Preparation																
Proposal Defense																

IRB, CPHS Approval																
Prepare instruments																
Prepare Survey Sites																
Train Study Staff																
Recruitment/ Data Collection																
Database Input																
Statistical Analysis																
Writing and Revisions																
Dissertation Defense																

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April 2, 2018

Fadlo Khuri, MD
Editor-in-Chief
Cancer

Dear Dr. Khuri:

I am submitting our manuscript, "Uncertainty in Illness and Health Literacy in Pancreatic Cancer Patients" for consideration of publication in your journal, *Cancer*. The dearth of information on uncertainty and health literacy in this patient population and scarcity of prior research on the relationship between these variables in the general population underscores the value of the research we have undertaken. We believe that the information and findings will be of interest to your readers, constructive to future research and beneficial to patient care.

The final manuscript has been read and approved by all authors. We look forward to your review and response.

Sincerely,

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Uncertainty in Illness and Health Literacy in Pancreatic Cancer Patients

Introduction

Uncertainty in illness is the inability to determine meaning of illness-related events (Mishel, 1988). It is a cognitive state that occurs when lack of cues leads to an inability to predict outcomes or meaningfully interpret experiences. *Health literacy* is the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Cutilli & Bennett, 2009; Dumenci et al., 2014). Despite a shared link to cognitive processing of health information suggested by their definitions, information on the association between uncertainty and health literacy is scarce. Neither uncertainty nor health literacy has been studied with a focus on pancreatic cancer patients whose illness experience is fraught with complex events that predispose to uncertainty and require proficient health literacy to manage effectively. This study was conducted to obtain information constructive to future research and patient care outcomes.

Background

Studies on uncertainty in multiple cancer populations have utilized Mishel's theoretical framework and suggest that uncertainty influences psychosocial adaptation and has been associated with diminished quality of life, emotional distress, perceived stress, lack of resourcefulness, and less emotional well-being (Kurita, Garon, Stanton, & Meyerowitz, 2013; Lin et al., 2015; Hagen et al., 2015; Zhang, 2017). Patients with cancer have been found to benefit from interventions addressing uncertainty (Mishel et al., 2009; Gil et al., 2006). Studies exploring uncertainty have been conducted on patients with breast cancer (Germino et al., 2013; Gil et al., 2006), prostate cancer (D. E. Bailey, Jr. et

al., 2011; D. E. Bailey, Mishel, Belyea, Stewart, & Mohler, 2004; Kazer, Psutka, Latini, & Bailey, 2013; Mishel et al., 2002; Mishel et al., 2009; Wallace, 2005), gynecological malignancies (McCorkle et al., 2009), renal malignancies (Parker et al., 2013), lymphoma (Elphee, 2008), and brain cancer (Cahill, Gilbert, & Armstrong, 2014; Cahill, Lin, et al., 2014; Lin et al., 2015). However, there are no published studies focusing on uncertainty in pancreatic cancer patients despite various factors in the pancreatic cancer experience that predispose to increased levels of uncertainty including the recalcitrant biology, grim prognosis, and lack of consistency in treatment sequence recommendations. Discovery of baseline information is required before testing and implementing uncertainty interventions found effective in other cancer populations.

Although uncertainty has been explored in patients with other aggressive malignancies, there are unique aspects to pancreatic cancer that warrant disease-specific investigation. Pancreatic cancer is the fourth leading cause of cancer deaths in the United States with 55,440 new cases and 44,330 deaths in estimated in 2018 (American Cancer Society [ACS], 2018). It has no established screening or prevention guidelines, no hallmark symptoms to promote early diagnosis and 80% of patients present with metastatic or locally-advanced disease at initial diagnosis (Chatterjee et al., 2012). Moreover, the widely-acknowledged high recurrence rate undermines confidence in achieving long-term survival. The low 5-year relative survival rate for pancreatic cancer of 8% (American Cancer Society, 2018) carries a forbidding outlook that can cause patients to become overly vigilant and mistakenly interpret symptoms unrelated to malignancy as indicators of recurrence.

For patients with localized disease, the 5-year survival rate is only 32% (American Cancer Society, 2018). In these patients who are eligible for curative resection, there is debate among experts regarding the sequence of therapy (Reynolds & Folloder, 2014; Evans et al., 2008; Varadhachary et al., 2008). While the National Comprehensive Cancer Network (NCCN) recommends upfront surgery for potentially-resectable disease (National Comprehensive Cancer Network, 2017), expert consensus and a number of phase II clinical trials support administration of neoadjuvant chemotherapy in selected patients with potentially-resectable, biopsy-proven adenocarcinoma prior to surgery (Halperin & Varadhachary, 2014; Evans et al., 2008; Varadhachary et al., 2008). The lack of conformity in treatment sequence recommendations can lead to confusion among patients seeking information and guidance in making treatment decisions. Conflicting information from clinicians on whether one should pursue upfront surgery versus neo-adjuvant therapy can present complex challenges that potentiate uncertainty and require a high level of health literacy to process.

Various factors contribute to uncertainty throughout the phases of care from the ambiguity at initial presentation, the complexity of treatment planning, the unpredictability of recurrence during survivorship, and the unfamiliarity with how things evolve at end-of life. A study that examined fear of recurrence in 240 patients with pancreatic and peri-ampullary tumors included 94 patients with pancreatic adenocarcinoma who completed treatment with curative intent and found that 37% of these patients reported frequent fearful thoughts, emotional disturbance, and functional impairment (Petzel et al., 2012). In a disease with vague distressing symptoms,

aggressive course, and complex treatments algorithms, it is necessary to assess precursors and identify ways to mitigate uncertainty.

As depicted in Figure 1, uncertainty is conceptualized as having antecedents namely the *stimuli frame*, the patient's *cognitive capacity*, and *structure providers* that include patient education, social support, and credible authority (Mishel, 1988). Stimuli frame comprises of event unfamiliarity, a lack of symptom pattern, and lack of event congruence experienced by patients during illness (Mishel & Braden, 1988). Structure providers are resources that help patients interpret variables in the stimuli frame. Structure providers include credible authorities, education, and social support (Mishel, 1988). Cognitive capacity refers to the patient's information-processing abilities that enable patients to make sense of their experience (Mishel et al., 2009). The theory suggests that an inability to form a cognitive structure allowing for interpretation of illness-related events can lead to uncertainty.

One factor not explicitly addressed in the framework is health literacy, defined by the Institute of Medicine and by the US Department of Health and Human Services as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Cutilli & Bennett, 2009; Dumenci et al., 2014). Concept analyses have ascribed reading and numeracy skills, comprehension, capacity to use information in health care decision-making, and successful functioning as a health care consumer as defining attributes of health literacy (Mancuso, 2008; Speros, 2005). Mancuso (2008) classifies the attributes in three categories with the first being *capacity* which involves the verbal, numerical, and social skills essential to advocating for oneself while negotiating the health care system.

The second is *comprehension* which involves the interaction of logic, language, and experience essential to interpretation of information. The third is c*ommunication* which involves intake, processing, output, and feedback of messages through speech, writing, or behavior. In addition to having these attributes, health literacy has been described as having three classes (Nutbeam, 2000). *Functional literacy* involves reading and writing skills for everyday situations while *interactive literacy* involves advanced cognitive skills combined with social skills that allows a person to extract information, derive meaning from different forms of communication and apply such to changing circumstances (Nutbeam, 2000). *Critical literacy* involves cognitive skills combined with social skills applied to critically analyze information and utilize such to exert greater control over life events (Nutbeam, 2000; Chinn, 2011).

The definition and conceptualization of health literacy suggest a link to uncertainty but their association has not been studied in cancer patients. A review of literature review did not yield any published research reports in this area. The search only revealed a conference abstract describing a pilot study in 25 hospitalized older adults with heart failure which showed a significant correlation (r = -.415; p = .039) between health literacy and uncertainty (Mock & Sethares, 2013). Another article discussed health literacy in advanced care planning in the context of proposing a theoretical model that posits improving health literacy skills and addressing domains of uncertainty can promote end-of-life discussions and decision making (Melhadho & Bushy, 2011). The dearth of information on the relationship of these variables and the lack of information on uncertainty and health literacy in the pancreatic cancer population underscore the significance of this study.

Health literacy has evolved into an essential component in efforts to improve health outcomes and is included in *Healthy People 2020* as an objective in the promotion of health communication (Office of Disease Prevention and Health Promotion; 2016). The promulgation of web-based medical information, shifts in health policy and system access, as well as advances in cancer care involve proficient health literacy to process appropriately. According to the US Department of Education, only 12% of English-speaking adults have proficient health literacy skills (Hepburn, 2012, US Department of Health and Human Services, 2010). If this holds true in the pancreatic cancer population, this is detrimental to care access and delivery as patients in this population are often required to navigate through complex information systems and interactions with clinicians in order to understand their illness, access appropriate services, and participate effectively in decision making.

There is a growing body of evidence suggesting that limited health literacy also negatively affects cancer prevention and disease management behaviors. A study on 1306 cancer patients found that when controlling for potentially confounding variables, an inverse relationship was found between health literacy and number of inpatient hospitalizations ($\beta = -0.041$, $p = .009$) as well as health literacy and total number of hospital days ($\beta = -0.028$. $p = .023$) (Cartwright et al, 2017). Studies in patients with colon cancer (Pendlimari, Holubar, Hassinger, & Cima, 2012), breast cancer (Buki, Yee, Weiterschan, & Lehardy, 2015; Halbach et al., 2015; Kamimura et al., 2016), cervical cancer (Sentell, Braun, Davis, & Davis, 2015), prostate cancer (Kayser, Hansen-Nord, Osborne, Tjonneland, & Hansen, 2015), lung cancer (Milne et al., 2015), and head and neck cancer (Koay et al., 2013) have also explored different aspects of health literacy and

the impact of poor literacy on outcomes. Review of Medline, Pubmed, CINAHL, and PsychINFO on health literacy and cancer outcomes revealed outcome studies on patients with various cancers including melanoma, colorectal cancer, prostate cancer, breast cancer, and lung cancer. The health outcomes investigated were quality of life (Husson, 2015; Song, 2012; Halverson, 2015; Milne, 2015), distress (Koay, 2013), decision satisfaction and regret over decision outcomes (Hawley, 2008), mental well-being (Song, 2012), medication adherence (Rust, 2011; Rust, 2012), sunscreen and sunbed use (Altsitsiadis, 2012), receipt of treatment including chemotherapy, reconstructive surgery, salvage hormone therapy, genetic counseling (Mahal, 2015; Busch, 2015: Winton, 2016), disease status at diagnosis (Wolf, 2006), and survivorship (Hulett, 2015). The results of the quantitative studies primarily support low health literacy as having a negative association with health outcomes and the results of the qualitative studies suggest that patients perceive low health literacy as a barrier to good outcomes.

The paucity of information on uncertainty and health literacy specific to the pancreatic cancer population is a hindrance to improving literacy and mitigating uncertainty. Because these factors may be modifiable and essential to improving care, it was important to address the information and research gap. The adapted model used for this study posits that health literacy could be a structure provider in the uncertainty framework (Figure 2).

Objectives

The purpose of the study was to evaluate uncertainty and health literacy in the pancreatic cancer patient population, determine an association between them, and evaluate predictors. The aims and hypotheses were:

1. Describe uncertainty using the Mishel Uncertainty in Illness Scale – Community instrument (MUIS-C) and health literacy using the Cancer Health Literacy Test – 30 (CHLT-30) in the pancreatic cancer population
2. Examine the association between uncertainty and health literacy in the pancreatic cancer patient population

   Hypothesis: Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients
3. Examine if health literacy is a significant predictor of uncertainty after adjusting for age, gender, race and ethnicity, education level, and disease treatment stage

   Hypothesis 3a: Health literacy is a significant predictor of uncertainty after adjusting for age, gender, education level, race and ethnicity, and disease treatment stage

   Hypothesis 3b: Education level, race, and disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients

Methods

Design

The study was conducted using observational, cross-sectional design. It was approved by the MD Anderson Cancer Center (MDACC) Institutional Review Board as well as by Committee for the Protection of Human Subjects of The University of Texas Health Science Center in Houston.

Variables and Measurements

Uncertainty was operationalized as the score on the MUIS-C (Appendix A), and health literacy operationalized as the score on the CHLT-30 (Appendix B). The MUIS-C has 23 items scored from 1 to 5 on a Likert scale. The item scores are summed with a

higher cumulative score indicating greater uncertainty. For the purpose of this study, cumulative scores on the MUIS-C were treated as continuous variables in accordance with developer intent. The MUIS-C has been used extensively with cancer patients. It was adapted from the 33-item Mishel Uncertainty in Illness Scale (MUIS-A), originally developed to evaluate uncertainty in acutely ill, hospitalized adults (Bailey et al., 2011). Items from the MUIS-A specifically relating to inpatient hospitalization were removed and the remaining questions comprise MUIS-C items. The MUIS-A was assessed for content analysis and its validation information was utilized to validate the MUIS-C (Bailey et al., 2011). In analyses of MUIS-C scores from 18 samples of chronically ill adults (total n=1068), Cronbach's alpha exceeded 0.85 in a large majority of the samples indicating the reliability of MUIS-C as comparable to the 0.87 reported for the MUIS-A (Bailey et al., 2011).

The 30-item CHLT-30 was created to assess literacy along the cancer health literacy continuum (Dumenci, et. al., 2014). It has been tested in 1,306 adults with heterogenous cancer diagnoses, educational attainment, as well as health insurance and marital status although pancreatic cancer was not specified as a category in the most common cancer types ascribed to these study participants (Dumenci at al., 2014). Reliability evidence for the CHLT-30 was a Cronbach's alpha of 0.88, McDonald's omega of 0.89, 2-week test–retest reliability of 0.90, and 6-month test–retest reliability of 0.90. There was support for the unidimensional scale and all variables had significant factor loadings of $\geq$ 0.44. Structural equation modeling supported external validity with self-confidence in engaging in health decisions specified as a latent variable measured by two positively and two negatively worded items. The developers indicated that it takes

10-15 minutes to complete the CHLT-30 electronically with a tablet device that also read the questions to patients. CHLT-30 score is the total number of correct responses and ranges from 0 to 30 (Dumenci, et. al., 2014).

The demographic information was obtained using a demographic form (Appendix C). Education was assessed by the highest level attained with the choices being "some high school", "completed high school", "vocational school", "some college", "completed college" "some graduate school" and "completed graduate school". Disease treatment phases included "before surgery", "within 2 years after surgery", "within 5 years after surgery", "5 years after surgery" and patients whose care did not include plans for resection were noted as "no surgery planned". The 2-year mark following surgery was selected to account for the high recurrence rate most frequently seen within 2 years following surgical resection (Heye, 2011). The 5-year mark was selected as this represents a widely-acknowledged and reported survival threshold.

In addition to the demographic and clinical information, the form also prompts inquiry into electronic devices used by the patient, if they use a mobile phone for purposes other than phone calls, and if they use the electronic health record to access their personal medical information.

Participants

Sample size justification was calculated using nQuery/nTerim version 3.0 assigning a two-sided type I error of 5% with 80% power to detect a correlation of 0.3 between uncertainty score and cancer health literacy score. It was determined that a sample of 82 participants was needed. A total 91 were invited with allowance for 10% attrition. The recruitment and accrual primarily occurred in surgical clinics. Patients

presenting to MDACC Gastrointestinal Clinic were screened for eligibility by the primary investigator who recruited eligible patients on a consecutive basis.

Eligibility Criteria

Eligibility criteria included patients with a diagnosis of pancreatic adenocarcinoma who are 18 years or older and receiving care in an MDACC outpatient clinic. Excluded were patients with pancreatic adenocarcinoma unable to speak, read, and write English. Patients with pancreatic adenocarcinoma who have evidence of active disease or have received oncologic treatment for another primary malignancy, except non-melanoma skin cancer, within the past 5 years were excluded.

Data Collection and Management

Recruitment and data collection schedules were coordinated with the clinical team. Patients were recruited, consented, and administered the questionnaires during clinic visits before being seen by the physician. The voluntary nature of participation, the study purpose, requirements and eligibility criteria were discussed. Informed consent was obtained via the electronic program used by MDACC for obtaining and storing consents in the electronic health record. The patient demographic form was completed with the patient and thereafter, the MUIS-C and CHLT-30 were administered through pen and paper approach according to protocol which called for the MUIS-C to be completed prior to the patients' visits with the physician. Participants were enrolled and issued a participant number using the Clinical Oncology Research System (CORe) program which serves as the MDACC institutional research management system. The primary investigator was present in clinic to collect the instruments at the conclusion of the patient's participation.

The MUIS-C and CHLT-30 were manually scored by the primary investigator according to the instrument manuals. After manual scoring, the responses were entered into a secure database developed using REDCap hosted by MDACC for data management. Questions and response options for the MUIS-C and CHLT-30 were programmed into REDCap with encoded formula that automatically generate scores based on entered participant responses. Every participant's REDCap score was compared with their manually-derived score and the REDCap entry was saved after a match between manually-derived and computer-generated scores was confirmed. The MUIS-C items that required reverse scoring were noted and programmed accordingly. Instrument hard copies were stored in secure files in the primary investigator's office.

Data Analysis

The REDCap database was exported to the IBM SPSS Statistics for Windows version 24 (IBM Corp). Significance for all tests were set at $p < .05$.

Descriptive analysis was used to describe uncertainty and health literacy as stated in Aim 1. Frequencies, percentages, central tendencies and variability measures were determined. Because CHLT-30 scores were found to be non-normally distributed, differences in group scores for both MUIS-C and CHLT-30 were analyzed using the non-parametric Kruskal Wallis test for the sake of consistency. Pair-wise testing with Bonferroni adjustment was used to ascertain where significant differences existed between levels of significant predictor groups.

To address Aim 2 Spearman Rho testing was used to evaluate the correlation between MUIS-C and CHLT-30 scores. This non-parametric test was selected due to the non-normality of the CLHT-30 scores distribution.

Aim 3a was addressed with multiple regression using the general linear model to determine if CHLT-30 score is an independent predictor of MUIS-C score accounting for age, gender, education, race and phase of care. Because a clear linear relationship between uncertainty and health literacy was not present, CHLT-30 scores were transformed into categorical predictors based on quantiles. Aim 3b tested the hypothesis that race/ethnicity, education level, disease treatment phase are significant predictors of MUIS-C and CHLT-30 scores. General linear model was used to test this hypothesis. The CHLT-30 score distribution violated the assumption of normality so an added measure utilizing bias corrected and accelerated bootstrap with 5,000 sampling iterations was incorporated into the analysis.

Results

Demographics and clinical characteristics

Ninety-one participants were enrolled and all had complete demographic data for age, marital status, racial/ethnic self-identification, gender, disease treatment phase, use of electronic devices and access utilization of their electronic health records. Of these, 82 completed both the MUIS-C and CHLT-30 and this group is used for analysis. The difference in the total and the evaluable samples was due in part to some participants not completing the instruments before being seen by the physician. There were also participants who decided not to complete instruments after starting for reasons that included not wanting to answer mathematic questions, being tired, instrument completion time being lengthy, or the health literacy questions being more difficult than anticipated.

As summarized in Table 1, the study sample (N=82) comprised of 45 males (55%) and 37 (45%) females with an average age of 64.59 years ranging from 30 to 80

years and were predominantly married (*n* = 61, 74%). Racial/ethnic self-identification was primarily White/Caucasian (*n* = 65, 79%) with Black/African American (*n* = 7, 8%), Asian (*n* = 4, 5%), and Latino/Hispanic (*n* = 7, 8%) comprising the remainder of the sample. The participants' education levels ranged from high school to completion of a graduate degree.

The sample primarily consisted of patients in surgical oncology clinics and the majority were receiving care in anticipation of eventual surgical resection (*n* = 40; 48%). The disease treatment phase composition also included patients within 2 years after surgery (*n* = 30, 37%), within 5 years after surgery (*n* = 5, 6%), 5 or more years after surgery (*n* = 2, 2%), and some with no surgery planned (*n* = 5, 6%). With respect to use of electronic devices, participants predominantly answered *yes* to owning a cellular phone (*n* = 81, 99%), reported using their phone for purposes other than phone calls (*n* = 78, 95%), and reported utilization of the electronic health record access to look up their medical information (*n* = 76, 93%).

This sample composition resembles that of the MDACC Surgical Oncology pancreatic adenocarcinoma database of patients who received care from 2000 - 2017. Of 8,875 patients, 56% in the database were male. Among the 8,763 patients who disclosed racial/ethnic self-identification, 77% were White/Caucasian and 76% of those who reported marital status were married.

Table 2 includes the sample means and medians along with variability measures. MUIS-C mean for this sample was 46.46 (*SD* = 12.94) with a median of 46.5 (*IQR* = 21). CHLT-30 mean was 26.65 (*SD* = 3.30) with a median of 28 (IQR = 4).

Group Differences

Kruskal Wallis testing revealed MUIS-C scores to be significantly different for levels of education (H = 15.44, p = .009), phase of care (H = 10.70, p = .030), and race/ethnic self-identification (H = 8.39 p = .039) as summarized in Table 3. The differences are detailed in Table 5 showing that the significance in education level (H = 44.16, p = .026) is between those whose highest educational attainment was high school (*Mdn* = 56.5, *IQR* = 17) and those who had some graduate schooling (*Mdn* = 35, *IQR* = 10*).* Post-hoc testing did not specify where the differences lie within phase of care. Significant difference in uncertainty scores within race/ethnic self-identification (H = 38.06, p = .024) was between Latino/Hispanics (*Mdn* = 36, *IQR* = 16) and Black/African Americans (*Mdn* = 54, *IQR* = 11).

CHLT-30 scores are summarized in Table 4 showing a significant difference for race/ethnic self-identification (H = 9.19, p = .0.27) but post-hoc pairwise testing did not show the source of the differences. There was a significant difference in CHLT-30 scores between education levels (H=18.33, p = .003) and post-hoc pairwise testing revealed significance (H= -29.75, p = .010) in the scores of those who completed high school as highest attainment (*Mdn* = 24.5; *IQR* 4) and those who completed college (*Mdn* = 28, *IQR* = 3). High school graduates also had significant difference in CHLT-30 scores (H= -25.82, p = .048) compared with those who attended some college (*Mdn* = 28, *IQR* = 4). Additionally, there was a significant difference (H = -49.20, p = .006) between high school graduates and those who attended some graduate school (*Mdn* = 29; *IQR* = 2) and a significant difference (H= -34.40, p = .010) in the scores between those who completed high school and those who completed a graduate degree (*Mdn* = 28.5, *IQR* = 2).

For the remainder of the analysis and reporting, education and disease treatment phase levels were re-classified to improve the balance of the group sizes. The vocational school participants (n = 3) were combined with those who attended some college (n = 26) as these levels are proximal to each other in the order of educational attainment and there was no significant difference in either the MUIS-C or CHLT-30 scores between the levels. They had the same CHLT-30 median of 28 and the MUIS-C score means for those who attended vocational school were closer to the score means of those who had some college than to those who completed high school (Table 3). The order of educational attainment as well as the score medians and means also factored into the decision to combine those who attended some graduate school (n = 4) with those who completed graduate degrees (n = 12).

Furthermore, due to only having two participants past the 5-year threshold in the disease phase category, they were combined with patients who were within 5-years after surgery. Of note, Kruskal Wallis analysis with post-hoc testing found no significant differences in the MUIS-C or CHLT-30 scores between participants within these two group levels. The phase of this new group was labeled *"2 or more years after surgery"*.

Correlation

Spearman Rho testing yielded a significant yet weak correlation between MUIS-C and CHLT-30 scores with a coefficient of $r_s(81) = -.24$ ($p = .032$). Education as an ordinal variable was also evaluated for its association with MUIS-C and CHLT-30 and had a statistically significant albeit weak correlation with uncertainty ($r_s(81) = .23$, $p = .038$) with health literacy ($r_s(81) = .38$, $p < .001$).

Predictors of Uncertainty

General linear model was utilized to assess significant predictors of uncertainty. Because of the non-linear relationship (Figure 3) between uncertainty and health literacy scores, the health literacy scores were transformed into quantiles for regression analysis. Histograms in Figure 4 depicted normality in the distribution of MUIS-C scores and of score residuals. Figure 5 shows the P-P Plot for distribution of residuals approximated linearity. For the actual scores, skewness of .22 (*SE* = .27), kurtosis of -.42, (*SE* = .53), and Shapiro Wilk test (p = .24) supported normality. Analysis of standardized residuals with a skewness of .16 (*SE* = .27), kurtosis of -.54 (*SE* = .53) and Shapiro Wilk (p = .47) also supported normality. The Levene's test (F = .93, p = .604) suggested homogeneity of variance. The profile plots of estimated marginal means for MUIS-C scores in Figure 6 had no intersecting lines suggesting no significant interactions between independent variables.

Health literacy was not a significant predictor of uncertainty (Table 6). General linear model testing revealed a significant corrected model (F(12, 69) = 3.23, p = .001), with an adjusted R^2 of .25 and η_p^2 = .360. A summary of findings in Table 6 shows that accounting for age, gender, education, disease treatment phase, and health literacy, the significant predictors of uncertainty are education (F(3, 69) = 6.36, p <.001, η_p^2 = .217), and phase of care (F(3,69) = 6.52, p = .001, η_p^2 = .221).

Table 7 specifies the differences in levels of the categorical variables compared with a reference in their groups. Within disease treatment phases, there was significant difference in the uncertainty scores between those without surgery planned and those who were within 2 years after surgery (B = -19.73; 95% CI = -31.14, -8.32; p = .001; η_p^2 =

.147). There was also a significant difference between those receiving treatment without planned surgery when compared with those who were at greater than 2 years after surgical resection (*B*= -26.66; 965% CI = -40.59, -12.74; $p < .001$; $\eta_p^{2 =} .175$) and those who were newly diagnosed but with potential for resection (*B*= -13.35; 965% CI = -2.42, -24.35; $p = .018$; $\eta_p^{2 =} .078$).

Within education levels, those whose highest attainment was completion of high school had a significant difference in uncertainty scores compared with each of the other education levels (Table 7). A significant difference was found between high school graduates and those who went on to some college or vocational school (*B* = -18.71; 95% CI = -28.07, -9.35; $p < .001$; $\eta_p^2 = .187$). There was also a significant difference among high school graduates and college graduates (*B* = -10.11; 95% CI = -19.34, -.87; $p < .032$; $\eta_p^{2 =} .065$) as well as high school graduates and those who attended or completed graduate school (*B* = -16.18; 95% *CI* = -26.49, -5.86; $p = .003$; $\eta_p^{2 =} .124$).

Predictors of Health Literacy

Histograms of the observed CHLT-30 scores and the standardized residuals using general linear model revealed a non-normal distribution (Figure 7). The observed scores had a skewness of -1.99 (*SE* = .27), kurtosis of 4.66 (*SE*= .53) and the Shapiro Wilk test of .79 ($p < .001$) all indicating normality violation. The standardized residuals had a skewness of .028 (*SE* = .27), kurtosis of 2.25 (*SE*= .53), and a Shapiro Wilk test of 82 ($p = .002$) indicating non-normality as well. The P-P plot showed a curvilinear pattern (Figure 8). Levene's test at $F = .865$ ($p = .633$) actually indicated equality in error variances. Given the negative skew of the observed scores, logarithmic transformation was not effective. Exponential, square, and cube transformation did not provide

appropriate correction. Multiple regression through general linear model was therefore performed with bias corrected and accelerated bootstrapping (BCa) method set at 5,000 iterations with the final results generated by SPSS indicating 4969 test samples. The profile plots of the estimated marginal means of the health literacy scores displayed no transections but rather parallel lines suggesting no significant interaction between independent variables (Figure 9).

The corrected model was significant ($F(8, 73) = 2.74$, $p = .011$), with an adjusted R^2 of .15 and $\eta_p^2 = .231$. A summary of findings in Table 8 shows that accounting for age, gender, education, and treatment phase, the significant predictors of health literacy is education ($F(3, 73) = 5.12$, $p = .003$, $\eta_p^2 = .174$). Table 9 details the differences in the levels of the categorical variables in comparison to a reference and shows the results of bias estimates from bootstrapping along with BCa 95% confidence intervals and standard errors with corresponding *p* values. Results of BCa in Table 9 show that those whose highest attainment was completion of high school had a significant difference in health literacy scores when compared to college graduates and those who attended or completed graduate school. High school graduates and those who completed college had a significant difference in health literacy scores without BCa at $p = .003$ ($B = 3.60$; 95% CI = 1.28; 5.91; $\eta_p^2 = .116$) and with BCa with $p = .001$ (BCa 95% CI = 1.82, 5.46; $SE = .98$; bias estimate -.02). High school graduates and those who attended or completed graduate school had a significant difference in health literacy scores without BCa at $p = .001$ ($B = 4.53$; 95% CI = 2.04; 7.02; $\eta_p^2 = .153$) and with BCa with $p < .001$ (BCa 95% CI = 2.68, 6.55; $SE = .98$; bias estimate .03).

Discussion

Uncertainty and Health Literacy

Based on the Uncertainty in Illness theory, the adapted model used for this study (Figure 2) proposes health literacy as a structure provider that can frame unfamiliar, incoherent, or destabilizing health experiences. It was hypothesized that the capacity to obtain and process basic health information and services needed to make appropriate health decisions has a significant inverse correlation with the cognitive inability to give meaning to health-related events.

Uncertainty levels in this study tended to be lower in reference to values summarized in the MUIS-C manual (N = 1068) with reported means of 42.4 – 85 and raw scores between 23 and 155. The mean for this present study (M = 46.44, SD = 12.94) approaches the lower end of the range reported in the manual. This is likely influenced by the education characteristics of the present study participants that predispose towards lower uncertainty. Health literacy scores trended higher in comparison with published research on health literacy using the CHLT-30. A study on health literacy and hospitalizations reported a CHLT-30 mean of 23.68 (SD = 5.52) (Cartwright, et al., 2017). The validation study for the CHLT-30 involving 1,306 cancer patients reported mean raw scores of 23.97 (SD=5.61) for men, 24.26 (SD=5.19) for women, 20.04 (SD=5.58) for non-Hispanic Blacks, and 26.61 (SD=3.38) for non-Hispanic Whites (Dumenci, et al., 2014). These values are lower than the overall (Table 2) and corresponding group mean scores (Table 4) from this study which is laden with participants from demographic groups that predispose to higher health literacy.

This study found a statistically significant correlation between uncertainty and health literacy suggesting an inverse association where uncertainty tends to decrease as health literacy increases. However, this was not a strong correlation ($r_s(81) = -.25$, $p = .031$). Although health literacy had a significant correlation with uncertainty, it actually had a stronger significant correlation with education ($r_s(81) = .39$, $p < .001$) which was a significant predictor of uncertainty along with phase of care. The interplay between these predictors likely factored in health literacy not maintaining its significance when adjusting for other variables. Health literacy is multifaceted and some of its qualities and effects may be shared with other variables thereby diminishing its individual influence in the overall model. It is interesting to consider this in light of research by Howard, Sentell, and Gazmararian (2006) in 3,260 participants to examine the extent to which low health literacy exacerbates differences between education levels and racial groups with respect to vaccination uptake and health status. Howard et al., found that health literacy explained a small to moderate portion of the differences that would have been attributed to education and race if health literacy were not considered (2006).

The results of this present study suggest while there is shared variance between variables, both uncertainty and health literacy have distinct characteristics that are not measured by other factors. Nonetheless, their interconnections merit further studies to bear out their influence in the patient's illness experience. The sample in the present study is relatively small with an over-representation of participants from groups with high literacy scores (White/Caucasians, higher levels of education attainment) and this imbalance can potentially obscure otherwise significant relationships and effects on uncertainty. Sample size and composition will be improved in future studies seeking to

clarify associations and further evaluating a prediction relationship between health literacy and uncertainty.

Effect of Education

Education level was found to be a significant predictor of uncertainty and health literacy in support of study hypotheses. The finding pertaining to health literacy is in accordance with a study on 402 smokers (Stewart, et. al, 2013) and with a study on 2,512 well-functioning older adults (Sudore, Mehta et al. 2006) that found low education level to be a significant predictor of low health literacy. It is also consistent with the findings of the landmark National Assessment of Adult Literacy whereby the US Department of Education evaluated adult literacy involving 19,000 participants (US Department of Education, 2006) that found average health literacy increased with each higher level of education attainment. The significant finding that education is a predictor of uncertainty is consistent with the summary in the MUIS-C manual that reports uncertainty scores decrease as education level increases (Mishel, 1997).

Education level was significant for MUIS-C and CHLT-30 in both Kruskal Wallis and general linear model testing. Education level is a predictor that suggests those whose highest attainment is high school completion have higher uncertainty and lower health literacy compared with participants at every other level of education attainment.

This study sample had 72 (87%) participants with post-high school education and 43 (52.4%) with a bachelor's degree or higher. For reference, only 33% of adults in the United States hold a bachelor's degree or higher (U.S. Department of Commerce, 2015). With this education composition, this study sample trended towards lower uncertainty scores and higher health literacy scores. This has practical value in helping identify

patients at risk for requiring special guidance in understanding their illness and engaging in their treatment decisions.

The study results also highlight the importance of distinguishing between education and health literacy and given the tendency to sometimes attribute health literacy levels based on education level, this underscores the importance of examining the unique aspects of each variable.

Effect of Race/Ethnicity

Race/Ethnicity was evaluated as a predictor but inferences and generalizability are restricted by the study sample comprising predominantly of White/Caucasian participants. According to the National Institutes of Health, the incidence of pancreatic cancer per 100,000 persons is 17 and 14.3 in Black/African males and females respectively compared with 14.2 and 11 in White males and females (National Institutes of Health, 2018). This highlights the need to conduct future research in settings that will allow for adequate representation of the diverse groups affected by this disease.

Phase of Care and Uncertainty

Disease treatment phase was a significant predictor of uncertainty in this study. Although pancreas cancer patients report frequent concerns about unpredictability of disease recurrence following treatment completion (Petzel, et al., 2013), uncertainty trended lower in patients who were further away from the time of their surgical resection compared with those who were closer to initial diagnosis. This is consistent with findings on evaluation of uncertainty predictors in brain tumor patients (Lin et al., 2015) where higher levels of uncertainty were found in patients closer to initial diagnosis. Pancreatic cancer patients in this study who were yet to undergo surgery had higher

uncertainty levels likely owing to the complexity and newness of the disease experience along with the concern that surgery may become a non-viable option if disease progresses or metastasis develops while on pre-operative treatment. However, patients who were close to initial diagnosis but determined to have unresectable disease and ineligible for curative resection had the highest levels of uncertainty. Surgical resection is the only treatment that bears potential for cure and being ineligible for curative treatment could predispose patients to a sense of disorganization and instability. The complexity of end-of-life concerns can also heighten uncertainty. Although patients who are receiving pre-surgery treatment are not guaranteed surgery, the possibility and hope for cure may be a mitigating factor for uncertainty. These findings are consistent with the Uncertainty of Illness theory that describes patient's cognitive appraisal of events as a danger or an opportunity (Figure 1). Uncertainty can diminish if uncertain situations have potentially favorable outcomes while threatening outcomes can amplify uncertainty (Mishel, 1990).

It was hypothesized that disease treatment phase would also have a significant influence on health literacy as the ability to access, understand, and utilize information could improve with more exposure to health information and services during the course of the care and treatment. This was not supported by the study but merits further evaluation with a larger sample that better represents heterogeneity in disease phases. A longitudinal study with repeat testing at the different phases can also be considered to find patterns of change while tracking the same patients for differences in health literacy levels through their disease course.

Technology Utilization

A majority of patients in this study reported owning a mobile phone that they used for purposes other than phone calls and also reported using the electronic health record system. This can also influence the mode of instrument administration in future studies with utilization of tablet or electronic administration instead of using pen and paper. The association of technology proficiency and health literacy can also be formally investigated in future studies.

Strengths and Limitations

This is the first study on uncertainty and health literacy focusing on pancreatic cancer patients. The study was conducted in a single-institution with participants who are predominantly White/Caucasian, mostly well-educated, married, and predominantly in the pre-surgical phase of treatment. The study generated valuable information but its homogenous sample restricts inferences and extrapolations especially with respect to effects of race/ethnicity. The high health literacy and low uncertainty levels in this sample may denote self-selection bias as participants with proficiency and resources that facilitate successful navigation of pathways towards receiving care in specialized centers may not be predisposed to high uncertainty or low health literacy. However, the small sample size may have also obscured significant relationships and effects that need larger samples to clarify.

The health literacy instrument was noteworthy. The CHLT-30 has advantages in that it is tailored for cancer patients across the health literacy continuum and is reliable and well-validated. Rather than merely screening for low health literacy or measuring the patient's perception of their health literacy, CHLT-30 actually measures knowledge,

skills, as well as confidence about engaging in health decisions. In doing so, the CHLT-30 can be lengthy with a degree of difficulty that can lead to bias as patients who are not confident with knowledge or test skills, and patients who are feeling poorly are more apt to defer or decline. Instruments that are highly reliable and well validated are critical but length of administration time and suitability to location and setting need consideration. In a high-volume and busy setting that involve an interdisciplinary team managing a highly-complex patient population, options should be carefully considered against research objectives. Future studies in similar settings should consider briefer instruments. Moreover, with the suggestion that patients in this setting have a high degree of technology utilization, electronic administration should be considered in future studies.

Despite the small sample size and lack of generalizability especially with respect to race/ethnicity, this study generated constructive follow-up research questions and provided useful information on identifying patients who require support with understanding their illness experience and those who require guidance with accessing information and services.

Summary and Future Directions

In conclusion, the present study describes valuable information on uncertainty and health literacy in pancreatic cancer patients as well as potential predictors. The data supported an inverse relationship between the uncertainty and health literacy but did not support health literacy as a significant predictor for uncertainty when accounting for other variables. The findings were consistent with prior research in showing that education level is a significant predictor for both uncertainty and health literacy. Moreover, the

study findings indicated support for disease treatment phase being a predictor for uncertainty.

Further research is needed to delineate the effects of education, race, and health literacy on uncertainty. Variables that mitigate uncertainty but disfavors enhancement of health literacy or vice versa also need to be studied. The effect of race and ethnicity need additional investigation as the race/ethnic composition of this sample limits extrapolation. Future studies will require larger sample sizes with adequate representation of demographic and clinical groups in order to uncover and clarify significant relationships that will help patients understand their illness experience and enhance knowledge, skills, as well as access to information and services.

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Table 1

Demographic Characteristics

Demographic Characteristic	**MUIS-C AND CHLT-30** ***N* = 82**
	n (%)
Age (mean) (range)	64.59 (50)
Gender	
• Male	45 (55%)
• Female	37 (45%)
Marital Status	
• Married	61 (74%)
• Single	8 (10%)
• Widowed	9 (11%)
• Married; currently separated	1 (1%)
• Unmarried; with significant other	3 (4%)
Racial and Ethnic Self-Identification	
• Asian	4 (5%)
• Black, African-American	7 (8%)
• Latino, Hispanic	6 (7%)
• White, Caucasian	65 (79%)
• Native American	-
• Native Hawaiian, Pacific Islander	-
Level of Education	
• Some High School	-
• Completed High School	10 (12%)
• Vocational School	3 (4%)
• Some College	26 (32%)
• Completed College	27 (33%)
• Some Graduate School	4 (5%)
• Complete Graduate Degree	12 (15%)
Phase of Care	
• Before Surgery	40 (49%)
• Within 2 Years After Surgery	30 (37%)
• Within 5 Years After Surgery	5 (6%)
• 5 or More Years After Surgery	2 (2%)
• No Surgery Planned	5 (6%)
Do you have cellular phone?	
• Yes	81 (99%)
• No	1 (1%)
Do you use cellular phone for purposes other than calls?	
• Yes	78 (95%)
• No	4 (5%)
Do you use electronic health record to access your medical information?	
• Yes	76 (93%)
• No	6 (7%)

Note. MUIS-C = Mishel Uncertainty in Illness Scale –Community; CHLT-30 = Cancer Health Literacy Test.

Table 2

MUIS-C and CHLT-30 Descriptive Statistics

		MUIS-C Scores	CHLT-30
N	Valid	82	82
	Missing	0	0
Mean		46.46	26.65
Std. Error of Mean		1.43	.365
95% CI	Lower	43.62	25.95
	Upper	49.28	27.37
Median		46.5	28.00
Std. Deviation		12.938	3.301
Range		60	16
Minimum		23	14
Maximum		83	30
IQR		21	4
Skewness		.22 (*SE* = .27)	-1.99 (*SE* =. 27)
Kurtosis		-.42 (*SE* = .53)	4.65 (*SE* =.53)

Note. MUIS-C = Mishel Uncertainty in Illness Scale –Community; CHLT-30 = Cancer Health Literacy Test 30; *SE* = standard error; *CI* = confidence interval; *IQR* = inter-quartile range.

Table 3

MUIS-C Results by Groups

Demographic Characteristic	n	Mean	SD	95% CI	Min	Max	Median	IQR	P value
Gender									(*H* = .17; *p* =.678)
• Male	45	47.07	12.98	43.17 - 50.97	25	83	47	21	
• Female	37	45.73	12.99	41.4 – 50.06	23	74	46	21	
Marital Status									(*H* = 1.72; *p* =.787)
• Married	61	45.72	12.48	42.52 - 48.92	23	70	46	24	
• Single	8	52.5	17.96	37.48 - 67.52	25	83	53	26	
• Widowed	9	47.89	13.33	37.64 – 58.13	26	74	51	14	
• Married; currently separated	1	45.69							
• Unmarried; w/ significant other	3	44.33	5.03	31.83 – 56.84	39	49	45	.	
Racial, Ethnic Self-Identification									(*H* = 8.39; *p* =.039)
• Asian	4	44.50	6.25	34.56 – 54.44	37	52	44.5	12	
• Black, African-American	7	56.14	7.73	48.99 – 63.3	48	70	54	11	
• Hispanic	6	36.5	9.27	26.77 – 46.23	26	50	36	16	
• White, Caucasian	65	46.46	13.32	43.16 – 49.76	23	83	46	22	
Level of Education									(*H* = 15.44; =.009)
• Completed High School	10	59	14.20	48.84 – 69.16	31	83	56.5	17	
• Vocational School	3	34.67	10.26	9.17 – 60.16	26	46	32	.	
• Some College	26	44.19	12.65	39.08 – 49.30	23	70	45	22	
• Completed College	27	47.89	11.02	43.53 – 52.25	27	67	48	20	
• Some Graduate School	4	34	5.29	25.58 – 42.42	27	39	35	10	
• Complete Graduate Degree	12	44.83	11.38	37.61 – 52.06	25	65	43	16	
Phase of Care									(*H* = 10.70; *p* =.030)
• Before Surgery	40	49.08	12.69	44.97 – 53.08	27	83	49.5	17	
• Within 2 Years After Surgery	30	42.57	12.54	37.88 – 47.25	23	67	42	20	
• Within 5 Years After Surgery	5	40	9.43	28.29 – 51.71	31	56	37	14	
• 5 or More Years After Surgery	2	39	18.38	-126.18 – 204.18	26	52	39	.	
• No Surgery Planned	5	58.4	8.26	48.14 – 68.66	50	70	59	16	

Note. P values generated using Kruskal Wallis analysis, H values represent Kruskal Wallis statistics. MUIS-C = Mishel Uncertainty in Illness Scale –Community. *n* = sample size, *SD* = standard deviation; *CI* = confidence interval*; Min* = lowest score*; Max* = highest score*; IQR* = inter-quartile range*; H* = Kruskal Wallis test statistic*;* Significance $p < 0.05$

Table 4

CHLT-30 Results by Groups

Demographic Characteristic	N	Mean	SD	95% CI	Min	Max	Median	IQR	P value
Gender									(*H* = 1.94; *p* =.164)
• Male	45	26.4	3.16	25.45 – 27.35	14	30	27	4	
• Female	37	26.95	3.48	25.79 – 28.11	14	30	28	3	
Marital Status									(*H* = 8.90; *p* =.063)
• Married	61	27.02	3.01	26.25 - 27.79	14	30	28	3	
• Single	8	24	3.07	21.43 – 26.57	19	28	25	5	
• Widowed	9	26	4.87	22.25 – 29.75	14	30	28	4	
• Married; currently separated	1	29							
• Unmarried w/ significant other	3	27.33	2.08	22.16 – 32.50	25	29	28	4	
Racial and Ethnic Self-Identification									(*H* = 9.19; *p* =.027)
• Asian	4	26.25	2.22	22.72 – 29.78	24	29	26	4	
• Black, African-American	7	21.71	7.09	15.16 – 28.27	25	30	19	15	
• Hispanic	6	24.17	3.55	20.45 – 27.89	18	28	24.5	6	
• White, Caucasian	65	27.43	2.00	26.94 – 27.93	21	30	28	3	
Level of Education									(*H* = 18.33; *p* = .003)
• Completed High School	10	23.6	2.72	21.66 – 25.54	18	27	24	4	
• Vocational School	3	27.67	.57	26.23 – 29.10	27	28	28	1	
• Some College	26	25.88	4.63	24.01 – 27.76	14	30	28	4	
• Completed College	27	27.52	1.63	26.88 – 28.16	25	30	28	3	
• Some Graduate School	4	29.00	.82	27.7 – 30.30	28	30	29	2	
• Complete Graduate Degree	12	27.83	1.85	26.66 – 29.01	24	30	28	2	
Phase of Care									(*H* = 1.97; *p* =.580)
• Before Surgery	40	25.95	4.06	24.65 – 27.25	14	30	27.50	5	
• Within 2 Years After Surgery	30	27.57	1.87	26.87 – 28.26	24	30	28	3	
• Within 5 Years After Surgery	5	26.80	2.39	23.84 – 29.76	23	29	28	4	
• 5 or More Years After Surgery	2	28	.	.	28	28	28	.	
• No Surgery Planned	5	26	4.06	20.96 – 31.04	19	29	28	6	

Note. P values generated using Kruskal Wallis analysis, H values represent Kruskal Wallis statistics. CHLT-30 = Cancer Health Literacy Test 30; *n* = sample size, *SD* = standard deviation; *CI* = confidence interval*; Min* = lowest score*; Max* = highest score*; IQR* = inter-quartile range*; H* = Kruskal Wallis test statistic*;* significance p < 0.05

Table 5

Levels Within Predictor Categories with Significant Differences on Kruskal Wallis Testing

	H	SE	Std. Test Statistic	Sig	Adj. Sig
MUIS-C SCORES					
EDUCATION					
• Completed HS/ Some Grad School	44.16	14.08	31.26	.002	.026
RACE					
• Latino – Black	38.06	13.24	2.87	.004	.024
PHASE OF CARE *					
CHLT-30 SCORES					
RACE*					
EDUCATION					
• Completed HS/Some College	-25.82	8.76	-2.95	.003	.048
• Completed HS/Completed College	-29.75	8.71	-2.42	.001	.010
• Completed HS/Some Grad School	-49.20	13.92	-3.54	.000	.006
• Completed HS/Completed Grad School	-34.41	10.07	-3.42	.001	.010

Note. * Variable was significant on Kruskall Wallis analysis but post-hoc testing did not reveal differences Post-hoc pair-wise testing was performed on all variables. Table only includes information on the pairs with significant differences; . CHLT-30 = Cancer Health Literacy Test 30; MUIS-C = Mishel Uncertainty in Illness Scale –Community; *H* = Kruskal Wallis test statistic; *SE* = standard error; *Std* = standardized; Adj. Sig = Bonferroni adjusted; Sig = $p < .05$

Table 6

General Linear Model Tests of Between Subjects – Effects with MUIS-C as Dependent Variable

	Type III Sum of Squares	df	F	Sig.	Partial Eta Squared
Corrected Model	4865.51	12	3.23	.001	.360
Intercept	3507.30	1	27.96	.000	.289
EDUCATION	2395.09	3	6.36	.001	.217
PHASECARE	2453.72	3	6.52	.001	.221
SEXGENDER	.01	1	.00	.993	.000
AGE	4.46	1	.04	.851	.001
CHLT-30	97.66	4	.20	.940	.011
Error	8656.88	69			
Total	190548.00	82			
Corrected Total	13522.39	81			

R Squared = .360 (Adjusted R Squared = .25)

Note. df = degrees of freedom; MUIS-C = Mishel Uncertainty in Illness; Scale –Community; CHLT-30 = Cancer Health Literacy Test 30

Table 7

General Linear Model Significant Differences in MUIS-C Scores Within Independent Variables

Corrected Model Summary		
Adjusted R^2	**F (df)**	**Sig.**	**Partial Eta Squared**
.248	3.23 (12,69)	p = <.001	η_p^2 = .360

Significant Differences in MUIS-C Scores Within Independent Variables							
				95% Confidence Interval			
	B	***SE***	***t***	**Lower Bound**	**Upper Bound**	***p***	**η_p^2**
Highest Education Attainment							
Completed High School							
Vocational/Some College	-18.71	4.69	-3.99	-28.07	-9.35	.000	.187
Completed College	-10.11	4.63	-2.18	-19.34	-.87	.032	.065
Some or Completed Grad	-16.18	5.17	-3.13	-26.49	-5.86	.003	.124
Gender							
Female *(Reference)*							
Male	.011	2.73	.00	-5.44	5.46	.997	.000
Disease Treatment Phase							
No Surgery Planned							
Before Surgery	-13.35	5.52	-2.42	-24.35	-2.35	.018	.078
Within 2 years After Surg	-19.73	5.72	-3.45	-31.14	-8.32	.001	.147
Greater 2 years from Surg	-26.66	7.00	-3.82	-40.59	-12.74	.000	.175
CHLT-30 SCORE							
CHLT -30 Score 30							
CHLT-30 Score 14 -25	1.14	4.92	.23	-8.68	10.95	.818	.001
CHLT -30 Score 26-27	-1.21	5.01	-.24	-11.19	8.80	.812	.001
CHLT -30 Score 28	.21	5.00	.04	-9.76	10.18	.967	.000
CHLT -30 Score 29	-1.94	4.81	-.40	-11.53	7.66	.688	.002
AGE	.03	.14	.19	-.24	.29	.851	.001

Note. df = degrees of freedom; *B* = unstandardized coefficient; η_p^2 = partial eta squared; *Sig* = significance; p < .05
MUIS-C = Mishel Uncertainty in Illness Scale –Community; CHLT-30 = Cancer Health Literacy Test

Table 8

General Linear Model Tests of Between Subjects – Effects with CHLT-30 as Dependent Variable

Source	Type III Sum of Squares	df	F	Sig.	Partial Eta Squared
Corrected Model	204.01	8	2.74	.011	.231
Intercept	1099.63	1	118.27	.000	.618
EDUCATION	142.84	3	5.12	.003	.174
PHASECARE	27.11	3	.97	.411	.038
SEXGENDER	11.68	1	1.26	.266	.017
AGE	6.82	1	.73	.395	.010
Error	678.73	73			
Total	59105.00	82			
Corrected Total	882.74	81			
R^2 = .23; Adjusted R^2 - .15					

Note. *df* = degrees of freedom; *B* = unstandardized coefficient; η_p^2 = partial eta squared; *Sig* = significance; $p < .05$
CHLT-30 = Cancer Health Literacy Test 30

Table 9

General Linear Model Significant Differences in CHLT-30 Scores Within Independent Variables

Corrected Model Summary								**Bootstrap Results**				
Adjusted R2	Type II Sum of Squares	F (df)		Sig.		Partial Eta Squared						
.15	204.01	2.74 (8,73)		p = <.011		η_p^2 = .231						
Differences in CHLT-30 Scores Within Independent Variables												
	B	*SE*	*t*	95% Confidence		*p*	η_p^2	Bias	*SE*	*P*	BCa 95% Confidence	
				Lower Bound	Upper Bound						Lower Bound	Upper Bound
Highest Level of Educational Attainment												
Completed High School *(Reference)*												
Vocational/Some College	2.31	1.18	1.96	-.04	4.67	.054	.050	.01	1.32	.095	-.36	4.91
Completed College	3.60	1.16	3.09	1.28	5.91	.003	.116	-.02	.98	.001	1.82	5.46
Some/Completed Grad School	4.53	1.25	3.63	2.04	7.02	.001	.153	.03	.98	.000	2.68	6.55
Gender												
Female *(Reference)*												
Male	-.81	.72	-1.12	-2.25	.63	.266	.017	-.04	.79	.315	-2.42	.57
Phase of Care/Treatment												
No Surgery Planned *(Reference)*												
Before Surgery	-.25	1.50	-.17	-3.23	2.73	.867	.000	.003	2.19	.918	-3.67	4.09
Within 2 years After Surgery	.94	1.54	.61	-2.13	4.00	.544	.005	.03	2.08	.665	-2.23	5.23
2 years After Surgery	1.04	1.88	.55	-2.70	4.78	.582	.004	.03	2.18	.631	-2.45	5.53

Note. Bias corrected and accelerated bootstrap calculation was set at 5,000 iterations with SPSS generating results based on 4969 samples. *df* = degrees of freedom; *B* = unstandardized coefficient; η_p^2 = partial eta squared; *Sig* = significance; p < .05

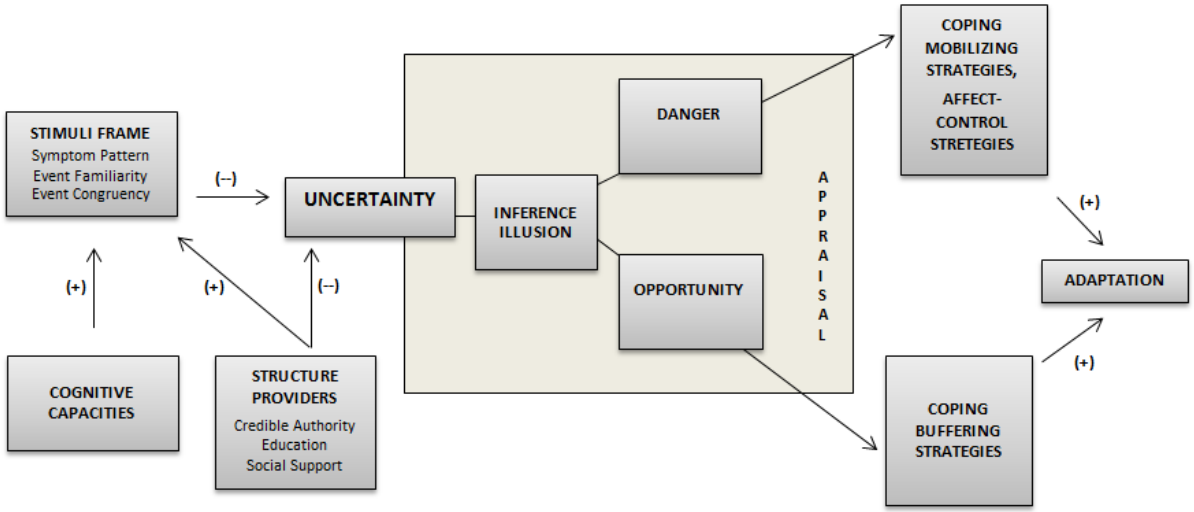

Figure1. Mishel's Uncertainty in Illness Model. Adapted from Uncertainty in Illness (Mishel, 1998)

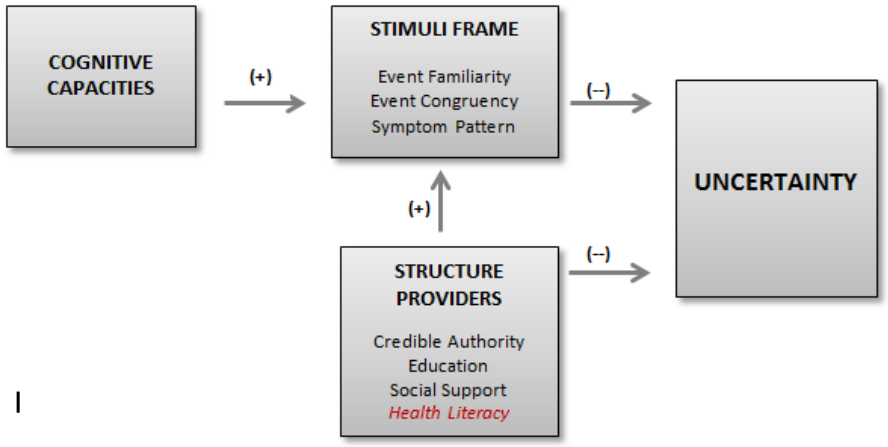

Figure 2. Antecedents to Uncertainty in Illness. Adapted from Uncertainty in Illness (Mishel, 1998)

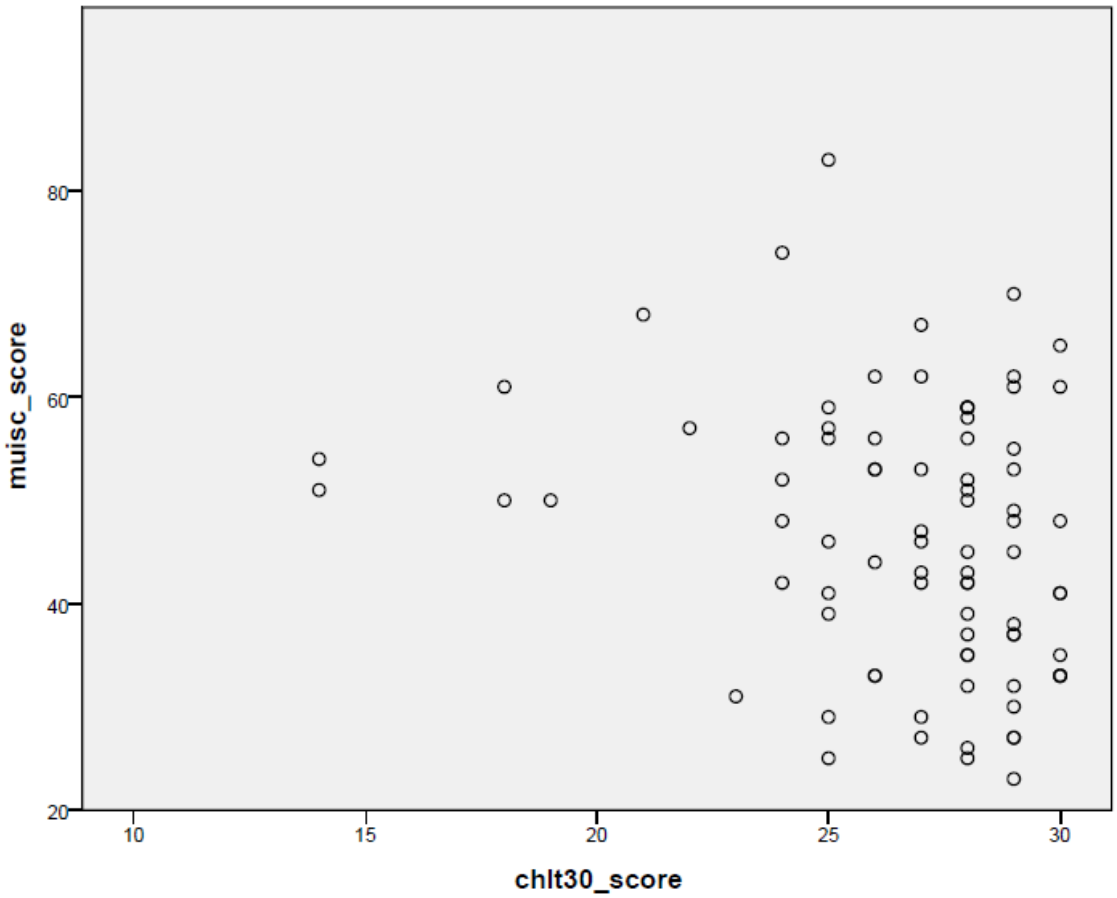

Figure 3. Scatterplot for MUIS-C and CHLT-30 Scores. MUIS-C = Mishel Uncertainty in Illness Scale –Community; CHLT-30 = Cancer Health Literacy Test 30

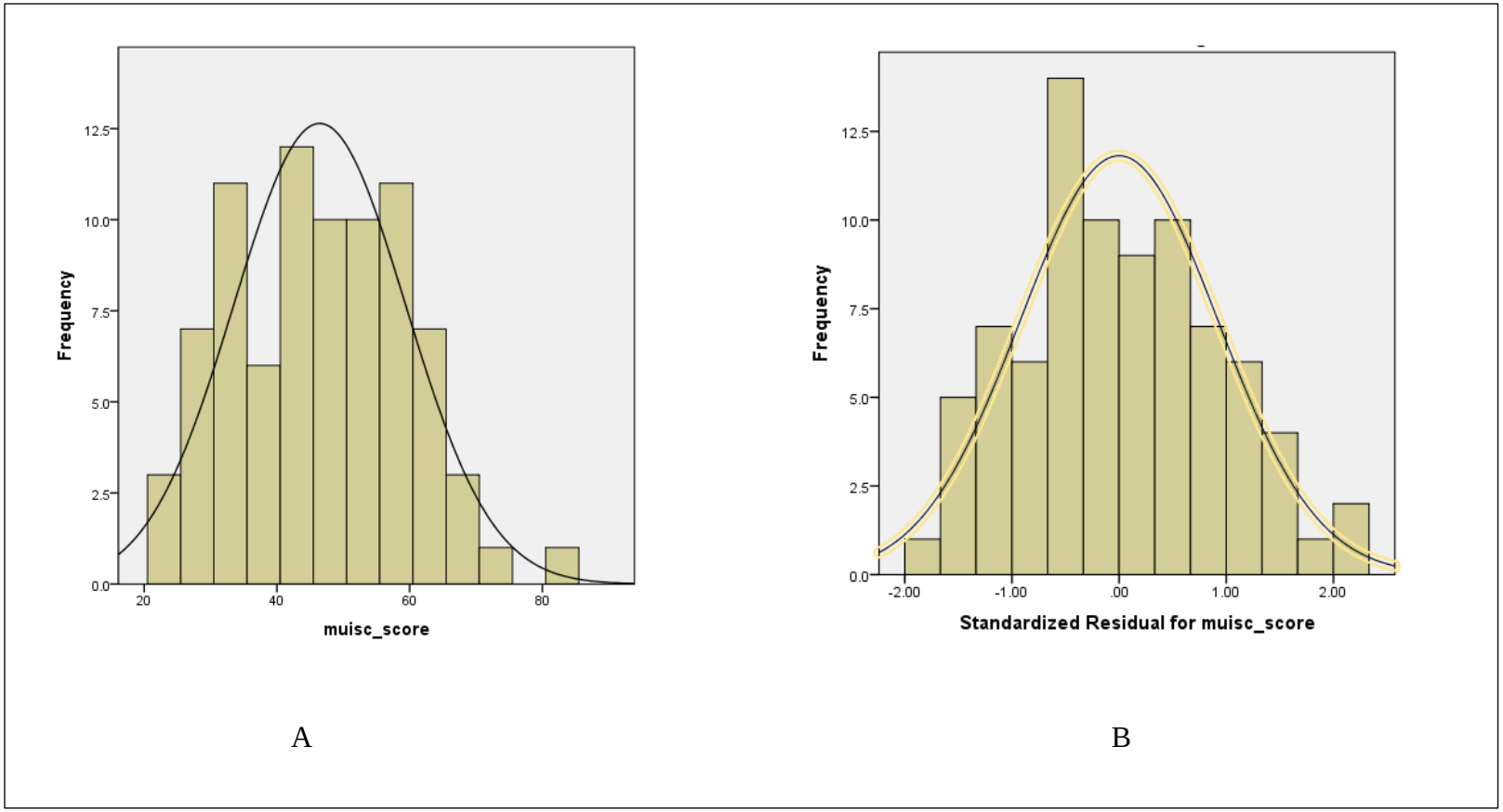

Figure 4. Histogram of MUIS-C observed scores and Histogram of MUIS-C Standardized Residuals. A = histogram of MUIS-C raw scores; B = histogram of MUIS-C standardized residuals. MUIS-C = Mishel Uncertainty in Illness Scale –Community

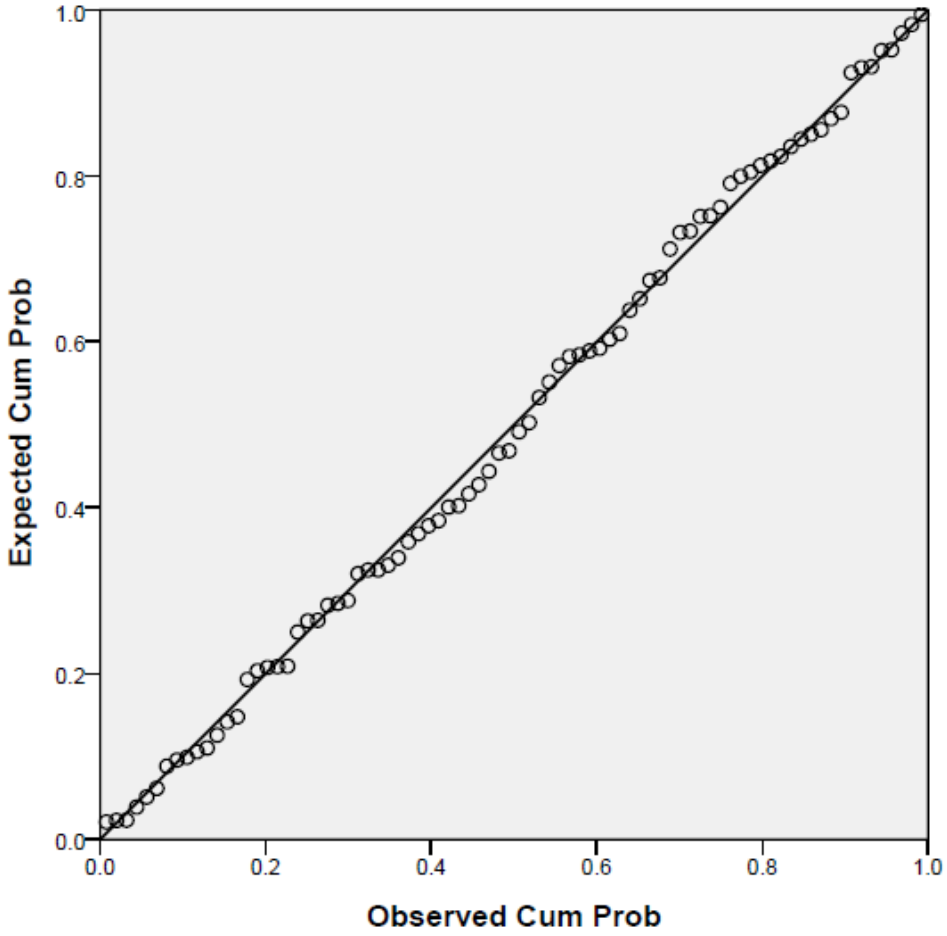

Figure 5. P-P Plot of Standardized Residuals for MUIS-C Scores. Probability plot of MUIS-C standardized residuals; MUIS-C = Mishel Uncertainty in Illness Scale –Community.

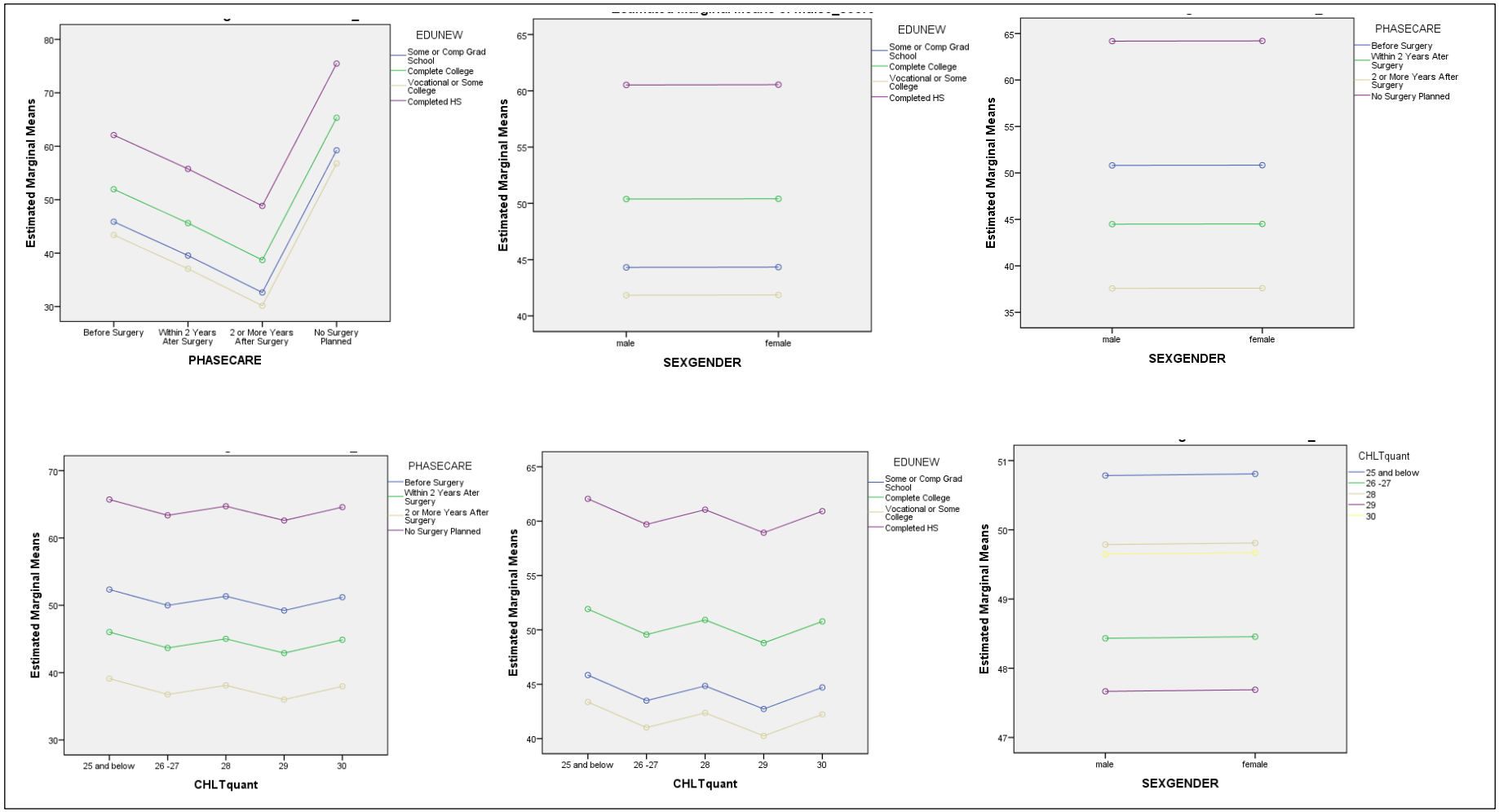

Figure 6. Estimated Marginal Means Profile Plots for MUIS-C. Covariates appearing in the model are evaluated at the following values: AGE = 64.59, chlt30_score = 26.65. No intersecting lines suggesting interaction were noted.

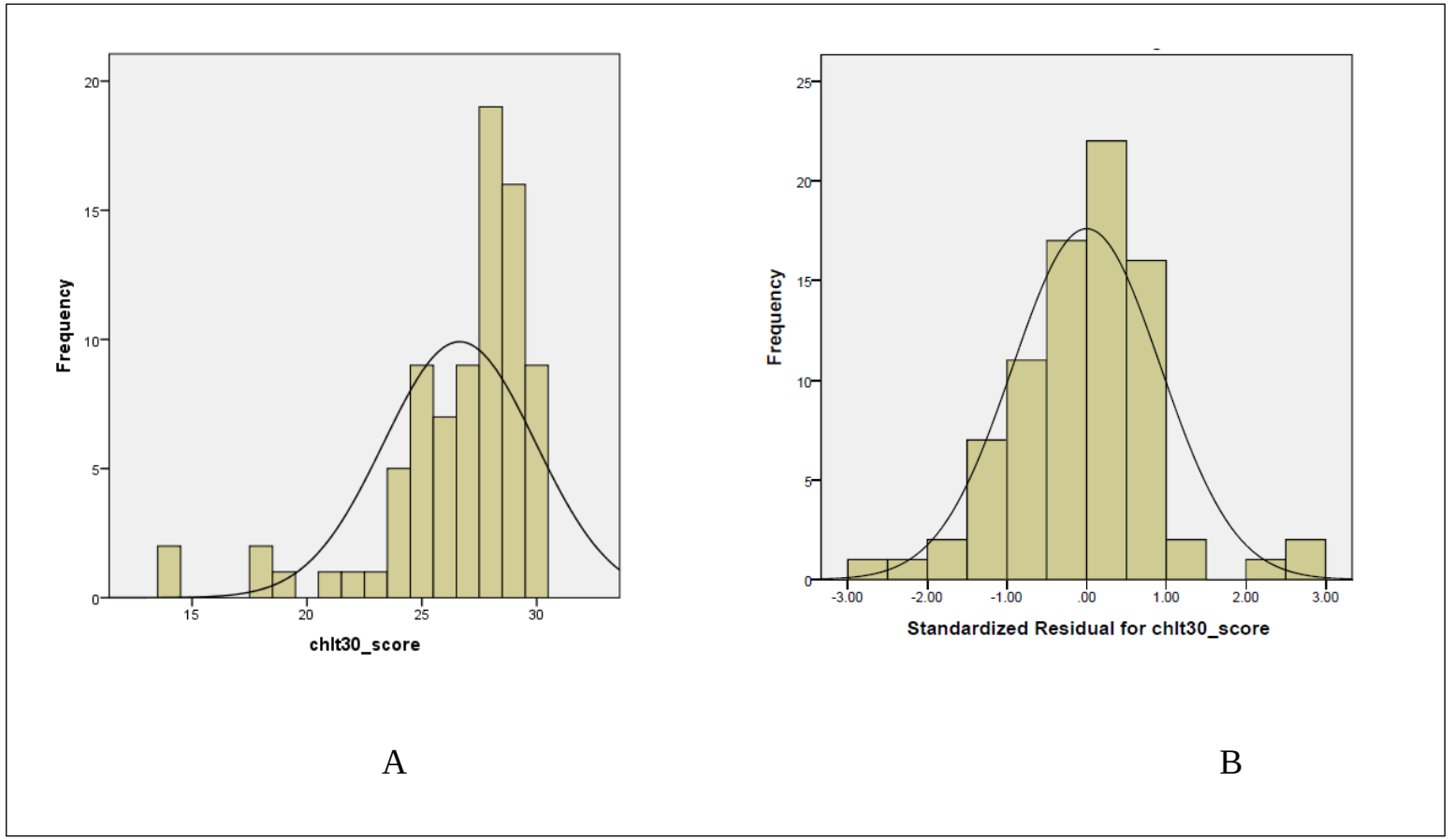

Figure 7. Histogram of CHLT-30 observed scores and Histogram of CHLT-30 Standardized Residuals. A = histogram of CHLT-30 raw scores; B = histogram of CHLT-30 standardized residuals. CHLT-30 = Cancer Health Literacy Test

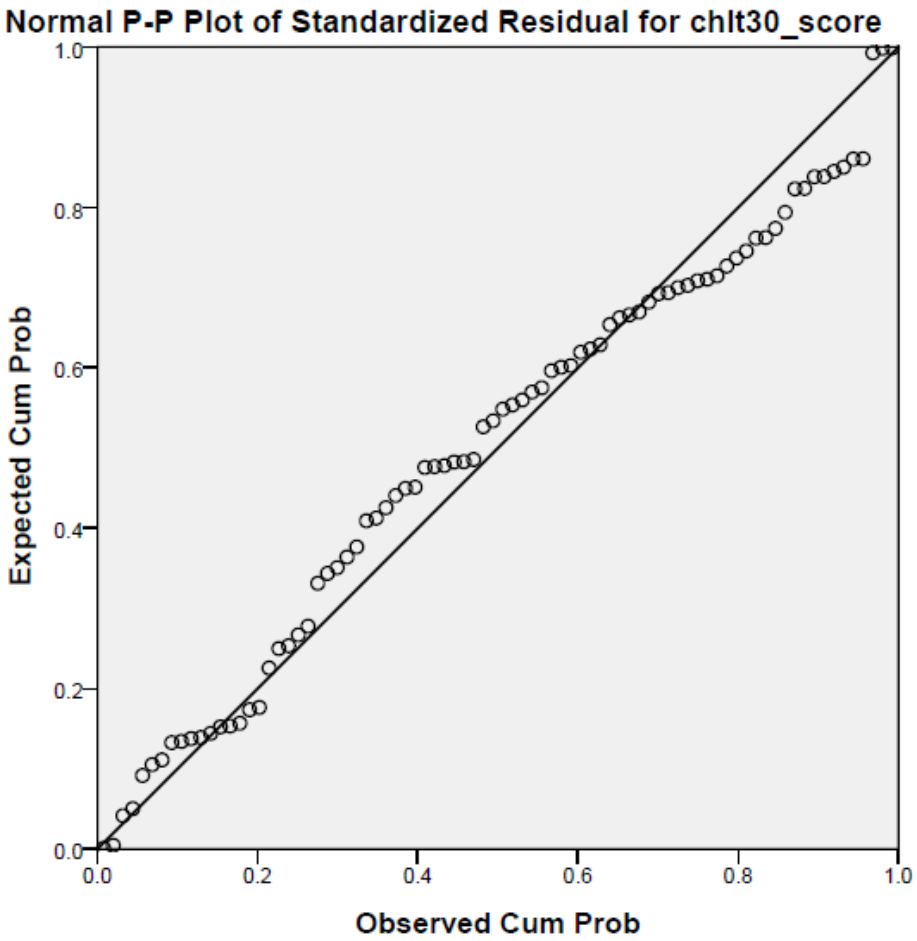

Figure 8. P-P Plot of Standardized Residuals for CHLT-30 Scores. Probability plot of standardized CLHT-30 residuals
CHLT-30 = Cancer Health Literacy Test

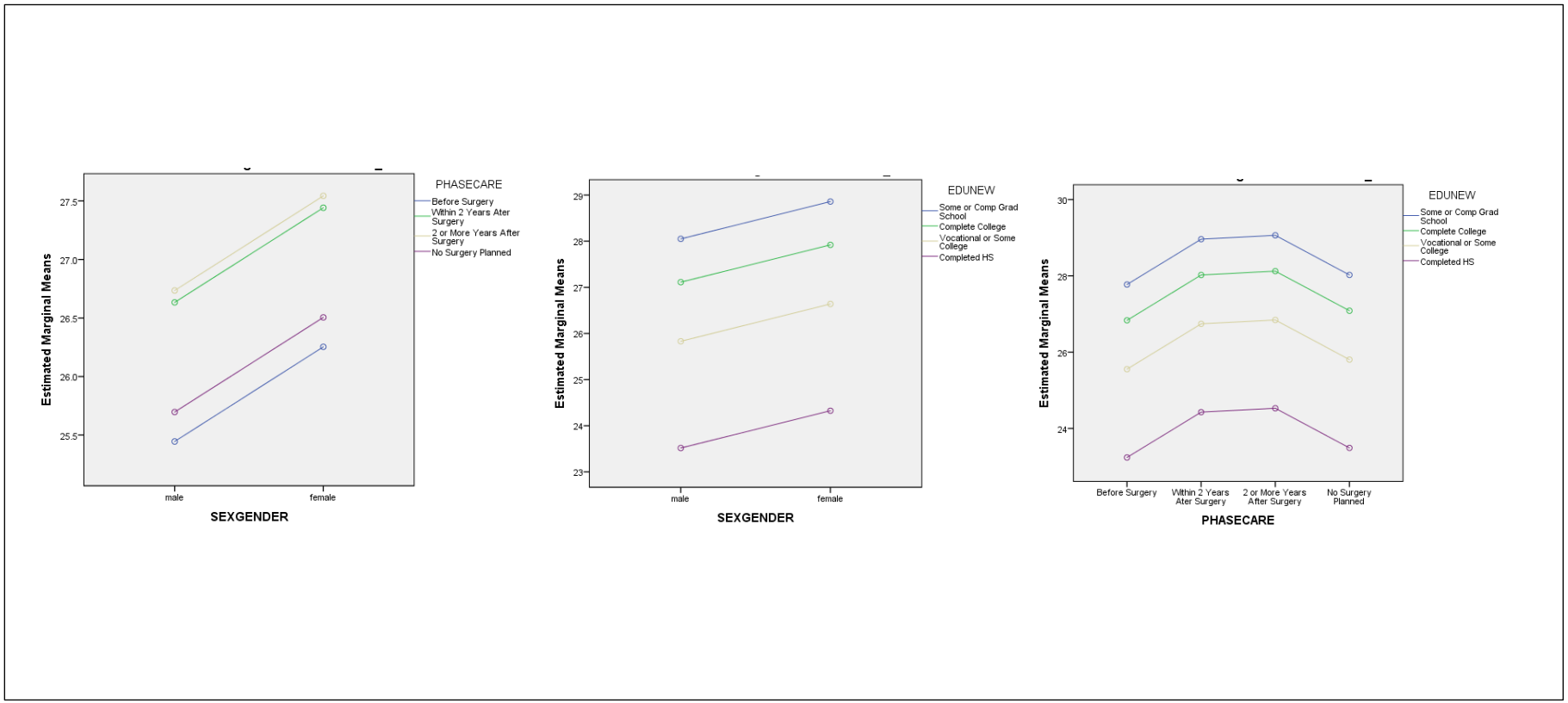

Figure 9. Estimated Marginal Means Profile Plots for CHLT-30. Covariates appearing in the model are evaluated at the following values: AGE = 64.59. No intersecting lines suggesting interaction were noted.

Appendix A

Approval of Proposal by Dissertation Committee (D2 Form)

UNIVERSITY OF TEXAS
HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF NURSING

Approval Form D-2

APPROVAL OF DOCTORAL DISSERTATION PROPOSAL

Student Principal Investigator: RAE BRIANA REYNOLDS

Title of Study: UNCERTAINTY & HEALTH LITERACY IN PANCREATIC CANCER PATIENTS

This research proposal has been reviewed and approved by the Principal Investigator's Dissertation Committee.

Committee Chair: GERI WOOD Date: 11/30/16

Committee Members:

TERRI ARMSTRONG Date: 11/30/16

[signature] Date: 11/30/16

Nikhil S Padhye Date: 11/30/16

Dissertation Committee Recommendation:

X Approval

_____ Approval with Reservations

_____ Disapproval

Original to Associate Dean for Academic Affairs; Copy to Chair, Committee members, and IRB(s)

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Appendix B

UT M.D. Anderson Cancer Center Approval from

Institutional Review Board

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Office of Protocol Research

Institutional Review Board (IRB)
Unit 1637
Phone 713-792-2933
Fax 713-794-4589

To: Rae Brana Reynolds 05/10/2017
From: David A. Kennedy
CC: Kristen L. Weaver, Lisa M. Kelly
MDACC Protocol ID #: 2017-0011
Protocol Title: Uncertainty and Health Literacy In Pancreatic Cancer Patients
Version: 04

Subject: Contingencies Met - Protocol 2017-0011

Official IRB Approval Date: 02/26/2017

On 05/09/2017 the Institutional Review Board 4 committee, chair, or designee granted approval to the above named and numbered protocol since the contingencies outlined by the IRB 4 on 02/26/2017 have been met.

It was noted that the protocol, informed consent documents (ICDs) and/or the Waivers of ICD and Authorization are satisfactory and in compliance with federal and institutional guidelines. No participants may be entered on this protocol until it has been officially activated by OPR.

In keeping with the requirements outlined in 45CFR46.109(e) and 21 CFR56.109(f), the IRB shall conduct continuing review of all protocols at intervals appropriate to the degree of risk, but not less than once per year.

You are responsible for promptly reporting to the IRB:

- any severe adverse events;
- any death while patient is on study;
- any unanticipated problems involving risks to subjects or others;
- any proposed changes in the research activity (changes may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects).

The IRB approval expiration date is 02/26/2018.

In keeping with the requirements outlined in 45CFR46.109(e) and 21 CFR56.109(f), the IRB shall conduct continuing review of all protocols at intervals appropriate to the degree of risk, but not less than once per year.

Please Note: The IRB made the determination that the request for DSMB waiver may be granted.

The IRB has made the determination that this study is low risk for continuing review and can be conducted through the expedited continuing review process.

To activate this study, please compose and send a "Request for Activation" memo in PDOL.

The existing Informed Consent and/or Waivers of Informed Consent and Authorization cannot be used until the protocol is Activated.

If a Material Transfer Agreement (MTA) is required, it must be obtained prior to Activation.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

David A. Kennedy 05/10/2017 04:08:03 PM

This is a representation of an electronic record that was signed and dated electronically and this page is the manifestation of the electronic signature and date:

David A. Kennedy
05/10/2017 04:06:30 PM
IRB 4 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015

From: Denise Olson
To: Reynolds,Rae; Weaver,Kristen L; Kelly,Lisa M
Subject: Activation and Distribution of Protocol 2017-0011
Date: Monday, May 22, 2017 5:00:31 PM

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Office of Protocol Research

Institutional Review Board (IRB)
Unit 1637
Phone 713-792-2933
Fax 713-794-4589

To: Rae Brana Reynolds 05/22/2017
From: Denise Olson
CC: Kristen L. Weaver, Lisa M. Kelly
MDACC Protocol ID #: 2017-0011
Protocol Title: Uncertainty and Health Literacy In Pancreatic Cancer Patients
Version: 04

Subject: Activation and Distribution of Protocol 2017-0011

This study is now active and ready for patient accrual.

The Informed Consent(s) will be available in the Informed Consent Printer Database within 30 minutes.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Denise Olson 05/22/2017 05:00:17 PM

This is a representation of an electronic record that was signed and dated electronically and this page is the manifestation of the electronic signature and date:

Denise Olson
05/22/2017 05:00:10 PM
IRB 4 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015

Appendix C

The University of Texas Health Science Center at Houston

Approval from the Committee on the Protection of Human Subjects

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

TO: Rae Zyn Reynolds
School of Nursing

FROM: Sylvia Romo
IRB Coordinator
CPHS Office

DATE: December 21, 2017

RE: HSC-SN-17-0454
Uncertainty and Health Literacy in Pancreatic Cancer Patients

Reference Number: 162837

Dear Rae Zyn Reynolds,
This site is not required to submit changes to the protocol as UTHealth IRB approved for MD Anderson to be the IRB of Record for this study.

If you have any questions please contact CPHS. No further action is required.

Appendix D

Protocol and IRB-Approved Amendments

MD Anderson Cancer Center Protocol 2017-0011

2017-0011
March 27, 2017

Uncertainty and Health Literacy In Pancreatic Cancer Patients

Study Chair: Rae Brana Reynolds, RN, ANP,

Department: Surgical Oncology

Phone: 713-792-6940

Unit: 1484

1.0 Objectives

1. Describe uncertainty in the pancreatic cancer patient population using the Mishel Uncertainty in Illness Scale – Community instrument (MUIS-C)
2. Describe health literacy using the Cancer Health Literacy Test – 30 (CHLT-30) and its association to uncertainty in the pancreatic cancer patient population
   Hypothesis 2a: Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients
   Hypothesis 2b: Health literacy is an independent predictor of uncertainty in pancreatic cancer patients after adjusting for age, sex, race, education level, and disease treatment stage
3. Examine if age, sex, race, education level, and disease treatment stage are significant predictors of uncertainty and health literacy in the pancreatic cancer population
   Hypothesis 3a: Education level, race, disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients
   Hypothesis 3b: Age and sex are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients

The primary aim is to determine if a significant correlation exists between of uncertainty and health literacy in the pancreatic cancer population (hypothesis 2a). As neither uncertainty nor health literacy has been studied in this population, exploratory aims are to describe uncertainty and health literacy in pancreatic cancer patients, and to examine for significant predictors.

2.0 Rationale

Pancreatic cancer has aggressive biology, vague and distressing symptoms, and lacks expert agreement on treatment guidelines for patients with potentially-curable, resectable disease. For patients undergoing treatment, there is debate even among experts regarding the sequence of therapy for patients with resectable disease (Evans et al., 2008; Varadhachary et al., 2008). The National Comprehensive Cancer Network (NCCI) recommends upfront surgery for potentially-resectable pancreatic cancer but expert consensus and a number of phase II clinical trials support administration of neoadjuvant chemotherapy in selected patients with biopsy-proven carcinoma prior to surgery (Halperin & Varadhachary, 2014). Even for patients who complete treatment, the widely-acknowledged high recurrence rate undermines confidence in having achieved long-term survival or cure. The 5-year survival rate for pancreatic cancer remains low at 7% (ACS, 2016) and approximately 80% of patients undergoing resection with curative intent develop distant metastasis or local recurrence within five years of surgery (Halperin & Varadhachary, 2014). With a grim prognosis, patients can become overly vigilant and mistakenly interpret symptoms unrelated to malignancy as indications of disease recurrence. All of these factors contribute to ***uncertainty***, defined as a cognitive state wherein there is inability to give meaning to illness events (Mishel, 1988, Mishel & Braden, 1988, Mishel, et al., 2009).). It is conceptualized by Mishel within the Uncertainty of Illness Theory as a cognitive state that occurs when the decision maker unable to assign values to events or is unable to predict outcomes due to cues being

lacking or insufficient (Bailey, et al., 2011). The framework describes that individuals cognitively process illness stimuli then through primary appraisal, derive meaning. Uncertainty has been studied in many cancer populations (Bailey et al., 2011; Cahill et al., 2014; Elphee, 2008; Germino et al., 2013; McCorkle et al., 2009; Mishel et al., 2002; Mishel et al., 2009; Parker et al., 2013) but it has not been studied in pancreatic cancer patients.

Uncertainty is linked to poor outcomes (Lin et al., 2015) and one factor that can potentially mitigate uncertainty is ***health literacy***, defined as the capacity to obtain, process, and understand health information and services needed to make appropriate health decisions (Dumenci, 2014). Limited health literacy is also associated with unfavorable outcomes in cancer patients (Mahal, 2015; Busch, 2015: Winton, 2016; Hawley, 2008; Koay, 2013) and low health literacy is perceived by cancer patients as a barrier to good outcomes (Rust, 2011; Rust, 2012). Unfortunately, health literacy has not been studied either with a focus on pancreatic cancer patients whose illness experience require navigation of complex information and services pathways in order to engage successfully in treatment decisions.

Despite the shared link to information processing suggested by their definitions, the relationship between uncertainty and health literacy has not been studied in cancer patients and has not been studied individually in pancreatic cancer patients. This study planned within a framework adapted from Mishel Uncertainty Theory will address these gaps (Mishel, 1988, Mishel & Braden, 1988, Mishel, et al., 2009). The model adapted from MIshel's orginal framework and focused on the antecedent portion of the original model is illustrated in Figure 1.

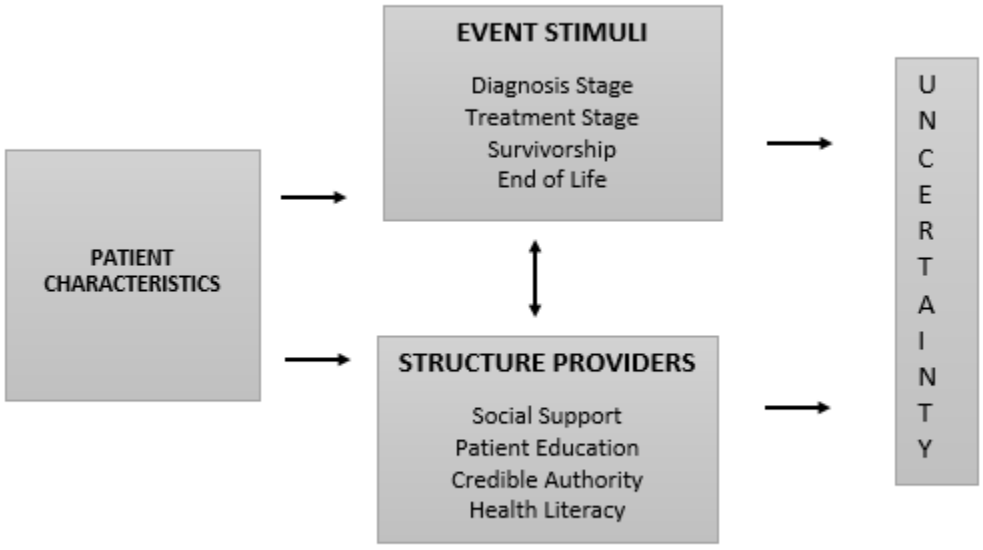

Figure 1. Antecedents of Uncertainty in Pancreatic Cancer Patients

Figure 1. Antecendents of Uncertainty in Pancreatic Cancer Patients Adapted from Mishel's Uncertainty in Illness Theory (Mishel, 1988).

In this model, Event Stimuli represents the events during the different phases of diagnosis and disease management that the patients may experience. The Structure Providers represent factors that can help the patient interpret illness events. Patient Characteristics include the patient's demographics that include age, education level, sex, and race. The study will examine demographic and factors to evaluate if there are predictors that can guide future research and identification of individuals who are more susceptible to uncertainty. Prior health literacy assessment in 1,306 cancer patients found no significant mean difference between men and women ($p=.247$) but the scores among African Americans were found to be significantly lower ($p < .0001$) than White participants (Dumenci et al., 2014). This study found that participants with limited health literacy consisted of an overrepresentation of African-Americans, patients who were undereducated, and patients with lower income (Dumenci et al., 2014). Meanwhile aggregate data on different population subgroups described in the Uncertainty in Illness Scales Manual indicate no difference in the mean scores based on sex or age but that scores decrease with an increase in level of education (Mishel, 1997). These demographic variables will be evaluated as this can influence the design and implementation of future studies and intended population of intervention programs. Moreover, patient uncertainty has been found to vary according to disease treatment stage with a brain tumor population study showing variation depending on treatment status with newly diagnosed patients and patients on active treatment having high levels of uncertainty (Lin et al., 2015). This will be assessed in pancreatic cancer patients to facilitate and promote communication between clinicians and patients when making health care decisions.

3.0 Eligibility of Subjects

INCLUSION CRITERIA

1. Patients with a diagnosis of biopsy-proven pancreatic adenocarcinoma who are being treated in an Ambulatory Outpatient Clinic at MD Anderson Cancer Center Main Campus.
2. Patients who meet the above criteria and are 18 years of age or older

EXCLUSION CRITETRIA

1. Patients who have a history or current diagnosis of another primary malignancy other than pancreatic adenocarcinoma
2. Patients unable to speak, read, or write in English will be excluded because the study instruments are in English
3. Pancreatic adenocarcinoma patients who are under 18 years of age

4.0 Research Plan and Methods

The study is designed as an observational, cross-sectional study seeking to describe uncertainty in illness and health literacy in the pancreatic cancer population and explore the relationship between these variables. Given the absence of prior studies on uncertainty and health literacy in pancreatic cancer patients, this design is appropriate as an exploration that can provide groundwork for future research. Written approval prior

to the initiation of the study will be obtained from the Institutional review Board of MD Anderson. The principal investigator (PI) will provide training to study staff prior to data collection.

Recruitment:
Patients who meet the eligibility criteria will be invited to participate in the study when they present for a clinic visit by the investigator and will be approached to obtain informed consent. This study and the recruitment will be conducted in the outpatient clinic during a patient's scheduled visit to the clinic. Patients will not be required to report to clinic for the purpose of study participation on days when they otherwise do not have a scheduled visit for cancer treatment or follow-up.

Collaboration and coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment. The eligibility review and recruitment will be as follows:

1. Primary investigator will pre-screen the patients scheduled to attend pancreatic cancer clinic in preparation for the research study
2. Primary investigator will send the list of eligible patients to the clinic team and obtain permission to recruit the patients in clinic on the day of their visits
3. Primary investigator will approach the eligible patients in clinic on a consecutive basis to explain the study and invite their participation
4. The primary investigator will explain the Informed Consent process and voluntary nature of study participation and address patient questions
5. The principal investigator will obtain signatures for Informed Consent
6. A copy of the completed consent will be kept in the electronic health record system
7. A copy of the completed consent will be offered to the patient and given to those who want to keep a copy for their personal records

Registration:

Enrolled patients will be registered into the Clinical Oncology Research System (CORe) which serves as the MD Anderson Cancer Center institutional patient data management system.

Data Collection:
The questionnaires will not contain identifiers but will only have a participant number. Enrolled patients will complete the instruments in the clinic. Collaboration and coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment.

The participants will complete the questionnaires in the clinic room or waiting area before they are seen by the physician during their visit.

1. Data will be collected by paper and pencil surveys with the investigator entering information into the web-based REDCap application hosted by MD Anderson Cancer Center (https://redcap.mdanderson.org)
2. The investigator or a clinical research staff will be available in clinic during the time the patient is completing the instruments
3. The investigator or research staff may not provide any answers to the specific questions on the questionnaire but can address questions about study participation or the process of form completion
4. Only the patient may complete the form. Family members or patient companions to the visit may not answer or complete the forms. If there are deficits that makes reading the questionnaire or writing the responses difficult, the questionnaire can be read to the patient by the research staff or the patient companion and the responses recorded according to the patient response
5. Investigator or research staff will review the forms to ensure completeness or that the participant has responded to all the items that want to answer. The primary investigator will keep the completed forms to a secure location in the primary investigator's office
6. Participants will not take home their questionnaires for completion. If a participant does not complete his or her participation while in clinic, the participant will not be included in the sample to be analyzed.

Recruitment and informed consents is anticipated to take 20 minutes while the time to complete the instruments is anticipated to take approximately 20 minutes with a total participation time of 40 minutes. The primary investigator will enter the data into the secure RedCap database. Data entry and instrument scoring will be conducted according to the instrument manuals and study protocol prepared for the study.

INSTRUMENTS

The Mishel Uncertainty in Illness Scale – Community Form (MUIS-C) will be used to measure uncertainty. The MUIS-C has 23 items scored 1 to 5 on a Likert scale. The item scores are summed with a higher cumulative score indicating greater uncertainty. The MUIS-C has been used extensively with cancer patients. The MUIS-C was adapted from the 33-item Mishel Uncertainty in Illness Scale (MUIS-A), originally developed to evaluate uncertainty in acutely ill, hospitalized adults (Bailey et al., 2011). Items from the MUIS-A specifically relating to inpatient hospitalization were removed and the remaining questions comprise the items for the MUIS-C version. The MUIS-A was developed through expert analysis and validation of the MUIS-A was utilized to support the validity of the MUIS-C (Bailey et al., 2011). In analyses of MUIS-C scores from 18 samples of chronically ill adults (total n=1068), Cronbach's alpha exceeded 0.85 in a large majority of the samples indicating the reliability of MUIS-C as comparable to the 0.87 reported for the MUIS-A (Bailey et al., 2011). Scores can range from 23 to 115 with a higher score indicating higher uncertainty. There is no categorical delineation regarding what is considered as "low", "moderate" or "high" uncertainty.

The Cancer Health Literacy Test – 30 (CHLT-30) (Dumenci, et. al., 2014) will be used to measure health literacy. The 30-item CHLT-30 was created to assess literacy along the cancer health literacy continuum. Its development was described in a publication of a study involving 1,306 adults with heterogenous cancer diagnoses, educational attainment, and health insurance and marital status. Pancreatic cancer was not listed as a category among the 11 diagnostic cancer types represented by the participants in the study sample. The reliability evidence for the CHLT-30 was a Cronbach's alpha of 0.88, McDonald's omega of 0.89, 2-week test–retest reliability of 0.90, and 6-month test–retest reliability of 0.90. There was support for the unidimensional scale and all variables had significant factor loadings of $\geq$ 0.44. Structural equation modeling supported external validity with self-confidence in engaging in health decisions specified as a latent variable measured by two positively and two negatively worded items. The test score is the total number of correct responses and ranges from 0 to 30. The instrument response time ranges from 10-15 minutes (Dumenci, et. al., 2014).
A Patient Demographic Form will be utilized to record demographic information including age, sex, education level, race, and disease treatment stage.
5.0 Statistics and Justification of Sample Size

The sample size calculation is based on the primary aim to determine a correlation between uncertainty and health literacy. An estimated total of up to 91 patients will be invited to participate. With an anticipated response rate of approximately 90%, an analyzable sample size of 82 will be produced. The primary objective is to collect the uncertainty and health literacy information in pancreatic cancer patients and assess the correlation between uncertainty and health literacy. The primary endpoints are the Mishel uncertainty scores, which is defined as the summation of all the questions scores and the cancer health literacy test scores which is defined as the number of questions that the patient answers correctly. With 82 patients in total, given the two-sided type I error of 5%, we will have an 80% power to detect a Pearson's correlation of 0.3 between uncertainty score and cancer health literacy score. nQuery/nTerim version 3.0 was used for the sample size justification.

Questionnaire scores will be calculated based on standardized manuals associated with each survey instrument. Descriptive statistics will be used to summarize scores of the questionnaires according to respective scoring manuals for each of the measures. The distribution of each continuous variable will be summarized by its mean, standard deviation, median, and range. The distribution of each categorical variable will be summarized in terms of its frequencies and percentages. The difference in uncertainty and health literacy scores will be assessed between groups (e.g. gender, education levels) by a two-sample t-test or ANOVA if the data is normally distributed; otherwise a Wilcoxon rank sum or Kruskal-Wallis test will be used. The association between uncertainty scores and health literacy score will be examined by Pearson correlation. To identify factors associated with uncertainty or health literacy scores of the survey measures, for example, the patient education level, age, race, and gender, multivariate linear regression will be performed to examine their effects.
Specifically, the hypotheses testing and anticipated results are as follows:

1. Describe uncertainty in the pancreatic cancer patient population using the MUIS - this primary, exploratory aim will assessed using Descriptive Analysis and Analysis of Variance (ANOVA)

2. Describe health literacy using the CHLT-30 and its association to uncertainty in the pancreatic cancer patient population
   Hypothesis 2a: **Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients** - Pearson product moment correlation coefficient will be calculated. Kendall's tau b or Spearman rho will be used if there is not a linear relationship or normal distribution. The anticipated result will be an inverse linear association between uncertainty and health literacy.
   Hypothesis 2b: **Health literacy is an independent significant predictor of uncertainty in pancreatic cancer patients after adjusting for age, sex, education level, race, disease treatment stage** - Health literacy will be included in multivariate regression to evaluate if it is a significant predictor of uncertainty after adjusting for other variables under study.

3. Examine significant demographic predictors of uncertainty and health literacy in the pancreatic cancer population
   Hypothesis 3a: Education level, race, disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients – Multiple linear regression will be performed to determine if these variables are significant predictors for uncertainty and multivariate regression will be also be performed to assess if they are significant predictors for health literacy as well. The anticipated results will be that education level, race, and disease treatment stage will be significant predictors for both health literacy and uncertainty.
   Hypothesis 3b: **Age and sex are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients** - Multivariate regression will be performed to determine if age and sex are significant predictors for uncertainty and multivariate regression will be also be performed assess if they are significant predictors for health literacy as well. The anticipated results will be that neither age not sex will come out as significant predictors for either uncertainty or health literacy.

6.0 Informed Consent Process

Participants 18 years of age and older will be consented in the clinic during scheduled visits. They will be consented by the study PI or by authorized, trained research personnel listed on the Delegation of Authority. This study has minimal risks and does not provide treatment.

Patients will be given the opportunity to review study documents and ask questions, and will be given time to consider their participation prior to signing the consent. This study is limited to English-speaking patients, due to the instruments only being available in English, therefore, patients who are unable to read, write, and understand English will not be consented to this study.

The investigator will acknowledge the patient's valuable contribution in participating in the study and explain the long-term goal of assessing the needs of pancreatic cancer patients to help clinicians enhance their communication skills and improve the way they engage patients in health care decisions.

7.0 Data Confidentiality:

The questionnaires will not contain identification information but only a participant number. Data will only be available to the PI and research team members directly involved with the collection and analysis of data related to this project. IRB approval will be obtained for any exchange of data outside of MD Anderson.

The members of the research team will be trained to maintain any patient health information confidential. Training will be documented as required by institutional policy.

Data Storage: The questionnaires will not contain identification information but only a participant number. The information key linking the participant number to his or her identification will be kept separate and secure. The PI and research staff will minimize risk by only storing information containing subject identifiers in locked file storage, on password-protected computers, and/or in a password protected database. In addition, access to patient identifiers will be limited to the minimum number of necessary research personnel, and only to those research personnel directly involved with obtaining patient information. Keys containing information linking study subjects to personal identifiers will be maintained in locked storage for paper records or behind institutionally approved firewall and electronic security measures for electronic keys, and available ONLY to the PI and research personnel. Information containing subject personal identifiers will not be removed from MD Anderson Cancer Center and will not be shared in publications or reports concerning this research study.

Data Sharing: Study data will not be shared with any individuals or entities that are not involved in the study. De-identified data may be shared with IRB-approved collaborating sites (PI's UT-Health Science Center Dissertation Committee). Sharing of data will be done only by secured mechanisms, as approved by MD Anderson Information Security.

Final disposition of study records: These data will be used only for this research study. Data that is in hard-copy form will be retained on site until the study is terminated, and may be stored indefinitely, per institutional standards, in long-term off-site storage with an MD Anderson approved, secured contract site. Electronic data will be retained indefinitely on MD Anderson servers behind the institutional firewall. Data will not be shared with any party outside of MD Anderson and will not be retained or disseminated for other research without prior IRB approval.

8.0 Distress Plan

Participants will be provided information on the benefits, and the importance of knowledge gained from the study. The voluntary nature of the study will be emphasized

and it will be explained to patients and clinicians that declination of participation in the study will not affect clinical treatment and/or care.
The Uncertainty in Illness Theory by Mishel defines uncertainty as a cognitive state wherein there is inability to assign value or meaning to illness-related events. Although Mishel conceptualized and designed the MUIS-C to measure a cognitive state and included no questions that address emotional distress, it is recognized that studes in a cancer population could be have associated distress. Since the MUIS-C manual does not delineate categories for low/moderate/high levels of uncertainty and because we do not know the levels of uncertainty in this population as it has not been previously studied, we cannot use the MUIS-C score to judge low-med-high uncertainty and assign a score that will prompt implementation of a distress plan. We will observe the patient for signs of unease or discomfort with the study and also review the responses so that items with answers that state "strongly agree" or for reservely scored items, those with "strongly disagree" will be reported to the clinical team so that the patient's uncertainty over their disease and management can be addressed.

The clinical team will also be notified if the patient verbalizes distress so that referral for counseling, supportive care, or psychiatry consult can be intiated. The patient will be informed that he/she may discontinue participation in the study at any time.

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Office of Protocol Research

Institutional Review Board (IRB)
Unit 1637
Phone 713-792-2933
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To: Rae Brana Reynolds 10/13/2017
From: Rosheta McCray
CC: Kristen L. Weaver, Lisa M. Kelly
MDACC Protocol ID #: 2017-0011
Protocol Title: Uncertainty and Health Literacy In Pancreatic Cancer Patients
Version: 05

Subject: Administrative IRB Approval – Protocol 2017-0011

On Tuesday, 10/03/2017, the Institutional Review Board (IRB) 4 chair or designee reviewed and approved your revision dated 09/13/2017 for Protocol 2017-0011

These Pages Include:

· Protocol Body – Document header Date: 09/13/2017
· Abstract Page – Document header Date: 09/13/2017

Revision included the following changes:
Updated the eligibility and the template.

Additional Revision History:
The PI submitted a revision on September 13, 2017 and it was approved contingent by an IRB 4 chair or designee. The PI responded to the IRB contingencies on September 28, 2017 and the response was approved by an IRB 4 chair or designee on October 3, 2017.

The revision can now be implemented. Please inform the appropriate individuals in your department or section and the collaborators of these changes.

Please Note: This approval does not alter or otherwise change the continuing review date of this protocol.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Rosheta McCray 10/13/2017 01:47:01 PM

This is a representation of an electronic record that was signed and dated electronically and this page is the manifestation of the electronic signature and date:

Rosheta McCray
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IRB 4 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015

2017-0011
Revised September 13, 2017

Uncertainty and Health Literacy In Pancreatic Cancer Patients

Study Chair: Rae Brana Reynolds, RN, ANP,

Department: Surgical Oncology

Phone: 713-792-6940

Unit: 1484

1.0 Objectives

1. Describe uncertainty in the pancreatic cancer patient population using the Mishel Uncertainty in Illness Scale – Community instrument (MUIS-C)

2. Describe health literacy using the Cancer Health Literacy Test – 30 (CHLT-30) and its association to uncertainty in the pancreatic cancer patient population
   Hypothesis 2a: Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients
   Hypothesis 2b: Health literacy is an independent predictor of uncertainty in pancreatic cancer patients after adjusting for age, sex, race, education level, and disease treatment stage
3. Examine if age, sex, race, education level, and disease treatment stage are significant predictors of uncertainty and health literacy in the pancreatic cancer population
   Hypothesis 3a: Education level, race, disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients
   Hypothesis 3b: Age and sex are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients

The primary aim is to determine if a significant correlation exists between of uncertainty and health literacy in the pancreatic cancer population (hypothesis 2a). As neither uncertainty nor health literacy has been studied in this population, exploratory aims are to describe uncertainty and health literacy in pancreatic cancer patients, and to examine for significant predictors.

2.0 Rationale

Pancreatic cancer has aggressive biology, vague and distressing symptoms, and lacks expert agreement on treatment guidelines for patients with potentially-curable, resectable disease. For patients undergoing treatment, there is debate even among experts regarding the sequence of therapy for patients with resectable disease (Evans et al., 2008; Varadhachary et al., 2008). The National Comprehensive Cancer Network (NCCI) recommends upfront surgery for potentially-resectable pancreatic cancer but expert consensus and a number of phase II clinical trials support administration of neoadjuvant chemotherapy in selected patients with biopsy-proven carcinoma prior to surgery (Halperin & Varadhachary, 2014). Even for patients who complete treatment, the widely-acknowledged high recurrence rate undermines confidence in having achieved long-term survival or cure. The 5-year survival rate for pancreatic cancer remains low at 7% (ACS, 2016) and approximately 80% of patients undergoing resection with curative intent develop distant metastasis or local recurrence within five years of surgery (Halperin & Varadhachary, 2014). With a grim prognosis, patients can become overly vigilant and mistakenly interpret symptoms unrelated to malignancy as indications of disease recurrence. All of these factors contribute to ***uncertainty***, defined as a cognitive state wherein there is inability to give meaning to illness events (Mishel, 1988, Mishel & Braden, 1988, Mishel, et al., 2009).). It is conceptualized by Mishel within the Uncertainty of Illness Theory as a cognitive state that occurs when the decision maker unable to assign values to events or is unable to predict outcomes due to cues being

lacking or insufficient (Bailey, et al., 2011). The framework describes that individuals cognitively process illness stimuli then through primary appraisal, derive meaning. Uncertainty has been studied in many cancer populations (Bailey et al., 2011; Cahill et al., 2014; Elphee, 2008; Germino et al., 2013; McCorkle et al., 2009; Mishel et al., 2002; Mishel et al., 2009; Parker et al., 2013) but it has not been studied in pancreatic cancer patients.

Uncertainty is linked to poor outcomes (Lin et al., 2015) and one factor that can potentially mitigate uncertainty is ***health literacy***, defined as the capacity to obtain, process, and understand health information and services needed to make appropriate health decisions (Dumenci, 2014). Limited health literacy is also associated with unfavorable outcomes in cancer patients (Mahal, 2015; Busch, 2015: Winton, 2016; Hawley, 2008; Koay, 2013) and low health literacy is perceived by cancer patients as a barrier to good outcomes (Rust, 2011; Rust, 2012). Unfortunately, health literacy has not been studied either with a focus on pancreatic cancer patients whose illness experience require navigation of complex information and services pathways in order to engage successfully in treatment decisions.

Despite the shared link to information processing suggested by their definitions, the relationship between uncertainty and health literacy has not been studied in cancer patients and has not been studied individually in pancreatic cancer patients. This study planned within a framework adapted from Mishel Uncertainty Theory will address these gaps (Mishel, 1988, Mishel & Braden, 1988, Mishel, et al., 2009). The model adapted from Mishel's original framework and focused on the antecedent portion of the original model is illustrated in Figure 1.

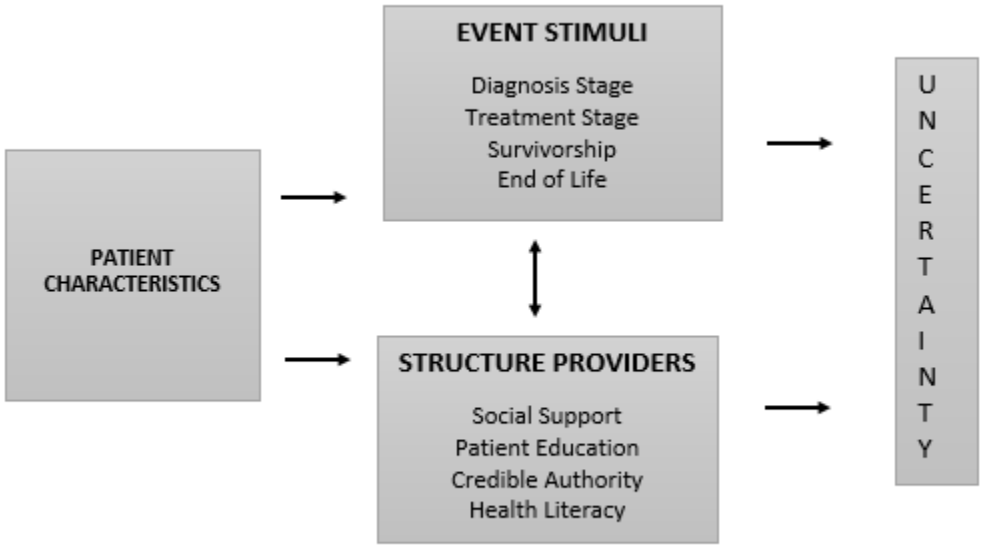

Figure 1. Antecedents of Uncertainty in Pancreatic Cancer Patients

Figure 1. Antecendents of Uncertainty in Pancreatic Cancer Patients Adapted from Mishel's Uncertainty in Illness Theory (Mishel, 1988).

In this model, Event Stimuli represents the events during the different phases of diagnosis and disease management that the patients may experience. The Structure Providers represent factors that can help the patient interpret illness events. Patient Characteristics include the patient's demographics that include age, education level, sex, and race. The study will examine demographic and factors to evaluate if there are predictors that can guide future research and identification of individuals who are more susceptible to uncertainty. Prior health literacy assessment in 1,306 cancer patients found no significant mean difference between men and women ($p=.247$) but the scores among African Americans were found to be significantly lower ($p < .0001$) than White participants (Dumenci et al., 2014). This study found that participants with limited health literacy consisted of an overrepresentation of African-Americans, patients who were undereducated, and patients with lower income (Dumenci et al., 2014). Meanwhile aggregate data on different population subgroups described in the Uncertainty in Illness Scales Manual indicate no difference in the mean scores based on sex or age but that scores decrease with an increase in level of education (Mishel, 1997). These demographic variables will be evaluated as this can influence the design and implementation of future studies and intended population of intervention programs. Moreover, patient uncertainty has been found to vary according to disease treatment stage with a brain tumor population study showing variation depending on treatment status with newly diagnosed patients and patients on active treatment having high levels of uncertainty (Lin et al., 2015). This will be assessed in pancreatic cancer patients to facilitate and promote communication between clinicians and patients when making health care decisions.

3.0 Eligibility of Subjects

INCLUSION CRITERIA

1. Patients with a diagnosis of biopsy-proven pancreatic adenocarcinoma who are being treated in an Ambulatory Outpatient Clinic at MD Anderson Cancer Center Main Campus
2. Patients with a diagnosis of pancreatic adenocarcinoma who also have a history of non-melanoma skin cancer(s) are eligible to participate
3. Patients who meet the above criteria and are 18 years of age or older

EXCLUSION CRITERIA

1. Patients with pancreatic adenocarcinoma who have a history or current diagnosis of another primary malignancy for which:
    - oncologic treatment is currently being administered or has been administered within past the five years
    - there has been evidence of disease within the past five years related to the patient's other malignancy

2. Patients unable to speak, read, or write in English will be excluded because the study instruments are in English
3. Pancreatic adenocarcinoma patients who are under 18 years of age

4.0 Research Plan and Methods

The study is designed as an observational, cross-sectional study seeking to describe uncertainty in illness and health literacy in the pancreatic cancer population and explore the relationship between these variables. Given the absence of prior studies on uncertainty and health literacy in pancreatic cancer patients, this design is appropriate as an exploration that can provide groundwork for future research. Written approval prior to the initiation of the study will be obtained from the Institutional review Board of MD Anderson. The principal investigator (PI) will provide training to study staff prior to data collection.

Recruitment:
Patients who meet the eligibility criteria will be invited to participate in the study when they present for a clinic visit by the investigator and will be approached to obtain informed consent. This study and the recruitment will be conducted in the outpatient clinic during a patient's scheduled visit to the clinic. Patients will not be required to report to clinic for the purpose of study participation on days when they otherwise do not have a scheduled visit for cancer treatment or follow-up.

Collaboration and coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment. The eligibility review and recruitment will be as follows:

1. Primary investigator will pre-screen the patients scheduled to attend pancreatic cancer clinic in preparation for the research study
2. Primary investigator will send the list of eligible patients to the clinic team and obtain permission to recruit the patients in clinic on the day of their visits
3. Primary investigator will approach the eligible patients in clinic on a consecutive basis to explain the study and invite their participation
4. The primary investigator will explain the Informed Consent process and voluntary nature of study participation and address patient questions
5. The principal investigator will obtain signatures for Informed Consent
6. A copy of the completed consent will be kept in the electronic health record system
7. A copy of the completed consent will be offered to the patient and given to those who want to keep a copy for their personal records

Registration:
Enrolled patients will be registered into the Clinical Oncology Research System (CORe) which serves as the MD Anderson Cancer Center institutional patient data management system.

Data Collection:
The questionnaires will not contain identifiers but will only have a participant number. Enrolled patients will complete the instruments in the clinic. Collaboration and coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment.
The participants will complete the questionnaires in the clinic room or waiting area before they are seen by the physician during their visit.

1. Data will be collected by paper and pencil surveys with the investigator entering information into the web-based REDCap application hosted by MD Anderson Cancer Center (https://redcap.mdanderson.org)
2. The investigator or a clinical research staff will be available in clinic during the time the patient is completing the instruments
3. The investigator or research staff may not provide any answers to the specific questions on the questionnaire but can address questions about study participation or the process of form completion
4. Only the patient may complete the form. Family members or patient companions to the visit may not answer or complete the forms. If there are deficits that makes reading the questionnaire or writing the responses difficult, the questionnaire can be read to the patient by the research staff or the patient companion and the responses recorded according to the patient response
5. Investigator or research staff will review the forms to ensure completeness or that the participant has responded to all the items that want to answer. The primary investigator will keep the completed forms to a secure location in the primary investigator's office
6. Participants will not take home their questionnaires for completion. If a participant does not complete his or her participation while in clinic, the participant will not be included in the sample to be analyzed.

Recruitment and informed consents is anticipated to take 20 minutes while the time to complete the instruments is anticipated to take approximately 20 minutes with a total participation time of 40 minutes. The primary investigator will enter the data into the secure RedCap database. Data entry and instrument scoring will be conducted according to the instrument manuals and study protocol prepared for the study.

INSTRUMENTS

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A Patient Demographic Form will be utilized to record demographic information including age, sex, education level, race, and disease treatment stage.
5.0 Statistics and Justification of Sample Size

The sample size calculation is based on the primary aim to determine a correlation between uncertainty and health literacy. An estimated total of up to 91 patients will be invited to participate. With an anticipated response rate of approximately 90%, an analyzable sample size of 82 will be produced. The primary objective is to collect the uncertainty and health literacy information in pancreatic cancer patients and assess the correlation between uncertainty and health literacy. The primary endpoints are the Mishel uncertainty scores, which is defined as the summation of all the questions scores and the cancer health literacy test scores which is defined as the number of questions that the patient answers correctly. With 82 patients in total, given the two-sided type I error of 5%, we will have an 80% power to detect a Pearson's correlation of 0.3 between uncertainty score and cancer health literacy score. nQuery/nTerim version 3.0 was used for the sample size justification.
Questionnaire scores will be calculated based on standardized manuals associated with each survey instrument. Descriptive statistics will be used to summarize scores of the questionnaires according to respective scoring manuals for each of the measures. The distribution of each continuous variable will be summarized by its mean, standard deviation, median, and range. The distribution of each categorical variable will be summarized in terms of its frequencies and percentages. The difference in uncertainty and health literacy scores will be assessed between groups (e.g. gender, education levels) by a two-sample t-test or ANOVA if the data is normally distributed; otherwise

a Wilcoxon rank sum or Kruskal-Wallis test will be used. The association between uncertainty scores and health literacy score will be examined by Pearson correlation. To identify factors associated with uncertainty or health literacy scores of the survey measures, for example, the patient education level, age, race, and gender, multivariate linear regression will be performed to examine their effects. Specifically, the hypotheses testing and anticipated results are as follows:

1. Describe uncertainty in the pancreatic cancer patient population using the MUIS - this primary, exploratory aim will assessed using Descriptive Analysis and Analysis of Variance (ANOVA)

2. Describe health literacy using the CHLT-30 and its association to uncertainty in the pancreatic cancer patient population
   Hypothesis 2a: **Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients** - Pearson product moment correlation coefficient will be calculated. Kendall's tau b or Spearman rho will be used if there is not a linear relationship or normal distribution. The anticipated result will be an inverse linear association between uncertainty and health literacy.
   Hypothesis 2b: **Health literacy is an independent significant predictor of uncertainty in pancreatic cancer patients after adjusting for age, sex, education level, race, disease treatment stage** - Health literacy will be included in multivariate regression to evaluate if it is a significant predictor of uncertainty after adjusting for other variables under study.

3. Examine significant demographic predictors of uncertainty and health literacy in the pancreatic cancer population
   Hypothesis 3a: Education level, race, disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients – Multiple linear regression will be performed to determine if these variables are significant predictors for uncertainty and multivariate regression will be also be performed to assess if they are significant predictors for health literacy as well. The anticipated results will be that education level, race, and disease treatment stage will be significant predictors for both health literacy and uncertainty.
   Hypothesis 3b: **Age and sex are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients** - Multivariate regression will be performed to determine if age and sex are significant predictors for uncertainty and multivariate regression will be also be performed assess if they are significant predictors for health literacy as well. The anticipated results will be that neither age not sex will come out as significant predictors for either uncertainty or health literacy.

6.0 Informed Consent Process

Participants 18 years of age and older will be consented in the clinic during scheduled visits. They will be consented by the study PI or by authorized, trained research personnel

listed on the Delegation of Authority. This study has minimal risks and does not provide treatment.

Patients will be given the opportunity to review study documents and ask questions, and will be given time to consider their participation prior to signing the consent. This study is limited to English-speaking patients, due to the instruments only being available in English, therefore, patients who are unable to read, write, and understand English will not be consented to this study.

The investigator will acknowledge the patient's valuable contribution in participating in the study and explain the long-term goal of assessing the needs of pancreatic cancer patients to help clinicians enhance their communication skills and improve the way they engage patients in health care decisions.
7.0 Data Confidentiality:

The questionnaires will not contain identification information but only a participant number. Data will only be available to the PI and research team members directly involved with the collection and analysis of data related to this project. IRB approval will be obtained for any exchange of data outside of MD Anderson.

The members of the research team will be trained to maintain any patient health information confidential. Training will be documented as required by institutional policy. Data Storage: The questionnaires will not contain identification information but only a participant number. The information key linking the participant number to his or her identification will be kept separate and secure. The PI and research staff will minimize risk by only storing information containing subject identifiers in locked file storage, on password-protected computers, and/or in a password protected database. In addition, access to patient identifiers will be limited to the minimum number of necessary research personnel, and only to those research personnel directly involved with obtaining patient information. Keys containing information linking study subjects to personal identifiers will be maintained in locked storage for paper records or behind institutionally approved firewall and electronic security measures for electronic keys, and available ONLY to the PI and research personnel. Information containing subject personal identifiers will not be removed from MD Anderson Cancer Center and will not be shared in publications or reports concerning this research study.

Data Sharing: Study data will not be shared with any individuals or entities that are not involved in the study. De-identified data may be shared with IRB-approved collaborating sites (PI's UT-Health Science Center Dissertation Committee). Sharing of data will be done only by secured mechanisms, as approved by MD Anderson Information Security. Final disposition of study records: These data will be used only for this research study. Data that is in hard-copy form will be retained on site until the study is terminated, and may be stored indefinitely, per institutional standards, in long-term off-site storage with an MD Anderson approved, secured contract site. Electronic data will be retained indefinitely on MD Anderson servers behind the institutional firewall. Data will not be

shared with any party outside of MD Anderson and will not be retained or disseminated for other research without prior IRB approval.

8.0 Distress Plan

Participants will be provided information on the benefits, and the importance of knowledge gained from the study. The voluntary nature of the study will be emphasized and it will be explained to patients and clinicians that declination of participation in the study will not affect clinical treatment and/or care.

The Uncertainty in Illness Theory by Mishel defines uncertainty as a cognitive state wherein there is inability to assign value or meaning to illness-related events. Although Mishel conceptualized and designed the MUIS-C to measure a cognitive state and included no questions that address emotional distress, it is recognized that studes in a cancer population could be have associated distress. Since the MUIS-C manual does not delineate categories for low/moderate/high levels of uncertainty and because we do not know the levels of uncertainty in this population as it has not been previously studied, we cannot use the MUIS-C score to judge low-med-high uncertainty and assign a score that will prompt implementation of a distress plan. We will observe the patient for signs of unease or discomfort with the study and also review the responses so that items with answers that state "strongly agree" or for reservely scored items, those with "strongly disagree" will be reported to the clinical team so that the patient's uncertainty over their disease and management can be addressed.

The clinical team will also be notified if the patient verbalizes distress so that referral for counseling, supportive care, or psychiatry consult can be intiated. The patient will be informed that he/she may discontinue participation in the study at any time.

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Office of Protocol Research

Institutional Review Board (IRB)
Unit 1637
Phone 713-792-2933
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To: Rae Brana Reynolds 12/01/2017
From: Rosheta McCray
CC: Kristen L. Weaver, Laura D. Henry
MDACC Protocol ID #: 2017-0011
Protocol Title: Uncertainty and Health Literacy In Pancreatic Cancer Patients
Version: 07

Subject: Administrative IRB Approval – Protocol 2017-0011

On Friday, 12/01/2017, the Institutional Review Board (IRB) 4 chair or designee reviewed and approved your revision dated 11/29/2017 for Protocol 2017-0011

These Pages Include:

· Protocol Body – Document header Date: 11/29/2017
· Abstract Page – Document header Date: 11/29/2017

Revision included the following changes:
Updated the Data Collection. Minor administrative change (abbreviations)

The revision can now be implemented. Please inform the appropriate individuals in your department or section and the collaborators of these changes.

Please Note: This approval does not alter or otherwise change the continuing review date of this protocol.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Rosheta McCray 12/01/2017 02:03:34 PM

This is a representation of an electronic record that was signed and dated electronically and this page is the manifestation of the electronic signature and date:

Rosheta McCray
12/01/2017 02:03:25 PM
IRB 4 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015

2017-0011
Revised November 29, 2017

Uncertainty and Health Literacy In Pancreatic Cancer Patients

Study Chair: Rae Brana Reynolds, RN, ANP,

Department: Surgical Oncology

Phone: 713-792-6940

Unit: 1484

1.0 Objectives

1. Describe uncertainty in the pancreatic cancer patient population using the Mishel Uncertainty in Illness Scale – Community instrument (MUIS-C)
2. Describe health literacy using the Cancer Health Literacy Test – 30 (CHLT-30) and its association to uncertainty in the pancreatic cancer patient population
   Hypothesis 2a: Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients
   Hypothesis 2b: Health literacy is an independent predictor of uncertainty in pancreatic cancer patients after adjusting for age, sex, race, education level, and disease treatment stage
3. Examine if age, sex, race, education level, and disease treatment stage are significant predictors of uncertainty and health literacy in the pancreatic cancer population
   Hypothesis 3a: Education level, race, disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients
   Hypothesis 3b: Age and sex are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients

The primary aim is to determine if a significant correlation exists between of uncertainty and health literacy in the pancreatic cancer population (hypothesis 2a). As neither uncertainty nor health literacy has been studied in this population, exploratory aims are to describe uncertainty and health literacy in pancreatic cancer patients, and to examine for significant predictors.

2.0 Rationale

Pancreatic cancer has aggressive biology, vague and distressing symptoms, and lacks expert agreement on treatment guidelines for patients with potentially-curable, resectable disease. For patients undergoing treatment, there is debate even among experts regarding the sequence of therapy for patients with resectable disease (Evans et al., 2008; Varadhachary et al., 2008). The National Comprehensive Cancer Network (NCCI) recommends upfront surgery for potentially-resectable pancreatic cancer but expert consensus and a number of phase II clinical trials support administration of neoadjuvant chemotherapy in selected patients with biopsy-proven carcinoma prior to surgery (Halperin & Varadhachary, 2014). Even for patients who complete treatment, the widely-acknowledged high recurrence rate undermines confidence in having achieved long-term survival or cure. The 5-year survival rate for pancreatic cancer remains low at 7% (ACS, 2016) and approximately 80% of patients undergoing resection with curative intent develop distant metastasis or local recurrence within five years of surgery (Halperin & Varadhachary, 2014). With a grim prognosis, patients can become overly vigilant and mistakenly interpret symptoms unrelated to malignancy as indications of disease recurrence. All of these factors contribute to ***uncertainty***, defined as a cognitive state wherein there is inability to give meaning to illness events (Mishel, 1988, Mishel & Braden, 1988, Mishel, et al., 2009).). It is conceptualized by Mishel within the Uncertainty of Illness Theory as a cognitive state that occurs when the decision maker unable to assign values to events or is unable to predict outcomes due to cues being

lacking or insufficient (Bailey, et al., 2011). The framework describes that individuals cognitively process illness stimuli then through primary appraisal, derive meaning. Uncertainty has been studied in many cancer populations (Bailey et al., 2011; Cahill et al., 2014; Elphee, 2008; Germino et al., 2013; McCorkle et al., 2009; Mishel et al., 2002; Mishel et al., 2009; Parker et al., 2013) but it has not been studied in pancreatic cancer patients.

Uncertainty is linked to poor outcomes (Lin et al., 2015) and one factor that can potentially mitigate uncertainty is ***health literacy***, defined as the capacity to obtain, process, and understand health information and services needed to make appropriate health decisions (Dumenci, 2014). Limited health literacy is also associated with unfavorable outcomes in cancer patients (Mahal, 2015; Busch, 2015: Winton, 2016; Hawley, 2008; Koay, 2013) and low health literacy is perceived by cancer patients as a barrier to good outcomes (Rust, 2011; Rust, 2012). Unfortunately, health literacy has not been studied either with a focus on pancreatic cancer patients whose illness experience require navigation of complex information and services pathways in order to engage successfully in treatment decisions.

Despite the shared link to information processing suggested by their definitions, the relationship between uncertainty and health literacy has not been studied in cancer patients and has not been studied individually in pancreatic cancer patients. This study planned within a framework adapted from Mishel Uncertainty Theory will address these gaps (Mishel, 1988, Mishel & Braden, 1988, Mishel, et al., 2009). The model adapted from MIshel's orginal framework and focused on the antecedent portion of the original model is illustrated in Figure 1.

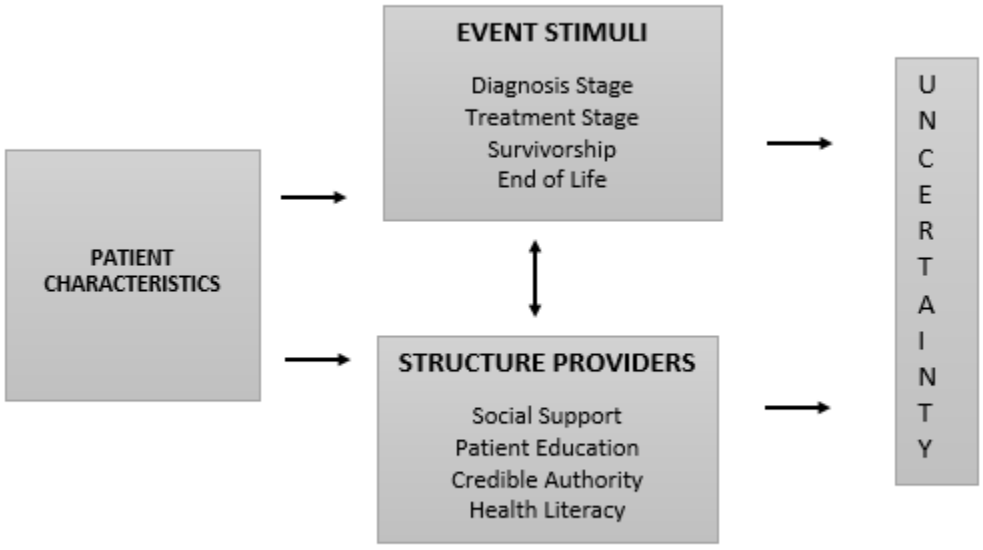

Figure 1. Antecedents of Uncertainty in Pancreatic Cancer Patients

Figure 1. Antecendents of Uncertainty in Pancreatic Cancer Patients Adapted from Mishel's Uncertainty in Illness Theory (Mishel, 1988).

In this model, Event Stimuli represents the events during the different phases of diagnosis and disease management that the patients may experience. The Structure Providers represent factors that can help the patient interpret illness events. Patient Characteristics include the patient's demographics that include age, education level, sex, and race. The study will examine demographic and factors to evaluate if there are predictors that can guide future research and identification of individuals who are more susceptible to uncertainty. Prior health literacy assessment in 1,306 cancer patients found no significant mean difference between men and women ($p=.247$) but the scores among African Americans were found to be significantly lower ($p < .0001$) than White participants (Dumenci et al., 2014). This study found that participants with limited health literacy consisted of an overrepresentation of African-Americans, patients who were undereducated, and patients with lower income (Dumenci et al., 2014). Meanwhile aggregate data on different population subgroups described in the Uncertainty in Illness Scales Manual indicate no difference in the mean scores based on sex or age but that scores decrease with an increase in level of education (Mishel, 1997). These demographic variables will be evaluated as this can influence the design and implementation of future studies and intended population of intervention programs. Moreover, patient uncertainty has been found to vary according to disease treatment stage with a brain tumor population study showing variation depending on treatment status with newly diagnosed patients and patients on active treatment having high levels of uncertainty (Lin et al., 2015). This will be assessed in pancreatic cancer patients to facilitate and promote communication between clinicians and patients when making health care decisions.

3.0 Eligibility of Subjects

Inclusion Criteria

1. Patients with a diagnosis of pancreatic adenocarcinoma who are being treated in an Ambulatory Outpatient Clinic at MD Anderson Cancer Center Main Campus
2. Patients with a diagnosis of pancreatic adenocarcinoma who are 18 years old or older

Exclusion Criteria

1. Patients with pancreatic adenocarcinoma who have:
    a. evidence of active disease, metastasis, or recurrence of another primary malignancy, except non-melanoma skin cancer, within the past 5 years
    b. a personal history of another primary malignancy, except non-melanoma skin cancer, for which oncologic treatment has been administered within the past 5 years
2. Patients unable to speak, read, or write in English
3. Pancreatic adenocarcinoma patients who are under 18 years of age

4.0 Research Plan and Methods

The study is designed as an observational, cross-sectional study seeking to describe uncertainty in illness and health literacy in the pancreatic cancer population and explore the relationship between these variables. Given the absence of prior studies on uncertainty and health literacy in pancreatic cancer patients, this design is appropriate as an exploration that can provide groundwork for future research. Written approval prior to the initiation of the study will be obtained from the Institutional review Board of MD Anderson. The principal investigator (PI) will provide training to study staff prior to data collection.

Recruitment:
Patients who meet the eligibility criteria will be invited to participate in the study when they present for a clinic visit by the investigator and will be approached to obtain informed consent. This study and the recruitment will be conducted in the outpatient clinic during a patient's scheduled visit to the clinic. Patients will not be required to report to clinic for the purpose of study participation on days when they otherwise do not have a scheduled visit for cancer treatment or follow-up.

Collaboration and coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment. The eligibility review and recruitment will be as follows:

1. Primary investigator will pre-screen the patients scheduled to attend pancreatic cancer clinic in preparation for the research study
2. Primary investigator will send the list of eligible patients to the clinic team and obtain permission to recruit the patients in clinic on the day of their visits
3. Primary investigator will approach the eligible patients in clinic on a consecutive basis to explain the study and invite their participation
4. The primary investigator will explain the Informed Consent process and voluntary nature of study participation and address patient questions
5. The principal investigator will obtain signatures for Informed Consent
6. A copy of the completed consent will be kept in the electronic health record system
7. A copy of the completed consent will be offered to the patient and given to those who want to keep a copy for their personal records

Registration:
Enrolled patients will be registered into the Clinical Oncology Research System (CORe) which serves as the MD Anderson Cancer Center institutional patient data management system.

Data Collection:
The questionnaires will not contain identifiers but will only have a participant number. Enrolled patients will complete the instruments in the clinic. Collaboration and

coordination with the clinic team seeing the patients will be established for the study prior to beginning screening, recruitment, and enrollment.

The participants will complete the MUIS-C questionnaires measuring uncertainty in the clinic room or waiting area before they are seen by the physician during their visit.

1. Data will be collected by paper and pencil surveys with the investigator entering information into the web-based REDCap application hosted by MD Anderson Cancer Center (https://redcap.mdanderson.org)
2. The investigator or a clinical research staff will be available in clinic during the time the patient is completing the instruments
3. The investigator or research staff may not provide any answers to the specific questions on the questionnaire but can address questions about study participation or the process of form completion
4. Only the patient may complete the form. Family members or patient companions to the visit may not answer or complete the forms. If there are deficits that makes reading the questionnaire or writing the responses difficult, the questionnaire can be read to the patient by the research staff or the patient companion and the responses recorded according to the patient response
5. Investigator or research staff will review the forms to ensure completeness or that the participant has responded to all the items that want to answer. The primary investigator will keep the completed forms to a secure location in the primary investigator's office
6. Participants will not take home their questionnaires for completion. If a participant does not complete his or her participation while in clinic, the participant will not be included in the sample to be analyzed.

Recruitment and informed consents is anticipated to take 20 minutes while the time to complete the instruments is anticipated to take approximately 20 minutes with a total participation time of 40 minutes. The primary investigator will enter the data into the secure RedCap database. Data entry and instrument scoring will be conducted according to the instrument manuals and study protocol prepared for the study.

INSTRUMENTS

The Mishel Uncertainty in Illness Scale – Community Form (MUIS-C) will be used to measure uncertainty. The MUIS-C has 23 items scored 1 to 5 on a Likert scale. The item scores are summed with a higher cumulative score indicating greater uncertainty. The MUIS-C has been used extensively with cancer patients. The MUIS-C was adapted from the 33-item Mishel Uncertainty in Illness Scale (MUIS-A), originally developed to evaluate uncertainty in acutely ill, hospitalized adults (Bailey et al., 2011). Items from the MUIS-A specifically relating to inpatient hospitalization were removed and the remaining questions comprise the items for the MUIS-C version. The MUIS-A was developed through expert analysis and validation of the MUIS-A was utilized to support the validity of the MUIS-C (Bailey et al., 2011). In analyses of MUIS-C scores from 18 samples of chronically ill adults (total n=1068), Cronbach's alpha exceeded 0.85 in a large majority of the samples indicating the reliability of MUIS-C as comparable to the

0.87 reported for the MUIS-A (Bailey et al., 2011). Scores can range from 23 to 115 with a higher score indicating higher uncertainty. There is no categorical delineation regarding what is considered as "low", "moderate" or "high" uncertainty.

The Cancer Health Literacy Test – 30 (CHLT-30) (Dumenci, et. al., 2014) will be used to measure health literacy. The 30-item CHLT-30 was created to assess literacy along the cancer health literacy continuum. Its development was described in a publication of a study involving 1,306 adults with heterogenous cancer diagnoses, educational attainment, and health insurance and marital status. Pancreatic cancer was not listed as a category among the 11 diagnostic cancer types represented by the participants in the study sample. The reliability evidence for the CHLT-30 was a Cronbach's alpha of 0.88, McDonald's omega of 0.89, 2-week test–retest reliability of 0.90, and 6-month test–retest reliability of 0.90. There was support for the unidimensional scale and all variables had significant factor loadings of ≥ 0.44. Structural equation modeling supported external validity with self-confidence in engaging in health decisions specified as a latent variable measured by two positively and two negatively worded items. The test score is the total number of correct responses and ranges from 0 to 30. The instrument response time ranges from 10-15 minutes (Dumenci, et. al., 2014). A Patient Demographic Form will be utilized to record demographic information including age, sex, education level, race, and disease treatment stage.

5.0 Statistics and Justification of Sample Size

The sample size calculation is based on the primary aim to determine a correlation between uncertainty and health literacy. An estimated total of up to 91 patients will be invited to participate. With an anticipated response rate of approximately 90%, an analyzable sample size of 82 will be produced. The primary objective is to collect the uncertainty and health literacy information in pancreatic cancer patients and assess the correlation between uncertainty and health literacy. The primary endpoints are the Mishel uncertainty scores, which is defined as the summation of all the questions scores and the cancer health literacy test scores which is defined as the number of questions that the patient answers correctly. With 82 patients in total, given the two-sided type I error of 5%, we will have an 80% power to detect a Pearson's correlation of 0.3 between uncertainty score and cancer health literacy score. nQuery/nTerim version 3.0 was used for the sample size justification.

Questionnaire scores will be calculated based on standardized manuals associated with each survey instrument. Descriptive statistics will be used to summarize scores of the questionnaires according to respective scoring manuals for each of the measures. The distribution of each continuous variable will be summarized by its mean, standard deviation, median, and range. The distribution of each categorical variable will be summarized in terms of its frequencies and percentages. The difference in uncertainty and health literacy scores will be assessed between groups (e.g. gender, education levels) by a two-sample t-test or ANOVA if the data is normally distributed; otherwise a Wilcoxon rank sum or Kruskal-Wallis test will be used. The association between uncertainty scores and health literacy score will be examined by Pearson correlation.

To identify factors associated with uncertainty or health literacy scores of the survey measures, for example, the patient education level, age, race, and gender, multivariate linear regression will be performed to examine their effects.

Specifically, the hypotheses testing and anticipated results are as follows:

1. Describe uncertainty in the pancreatic cancer patient population using the MUIS - this primary, exploratory aim will assessed using Descriptive Analysis and Analysis of Variance (ANOVA)

2. Describe health literacy using the CHLT-30 and its association to uncertainty in the pancreatic cancer patient population
   Hypothesis 2a: **Higher levels of health literacy are significantly correlated with lower levels of uncertainty in pancreatic cancer patients** - Pearson product moment correlation coefficient will be calculated. Kendall's tau b or Spearman rho will be used if there is not a linear relationship or normal distribution. The anticipated result will be an inverse linear association between uncertainty and health literacy.
   Hypothesis 2b: **Health literacy is an independent significant predictor of uncertainty in pancreatic cancer patients after adjusting for age, sex, education level, race, disease treatment stage** - Health literacy will be included in multivariate regression to evaluate if it is a significant predictor of uncertainty after adjusting for other variables under study.

3. Examine significant demographic predictors of uncertainty and health literacy in the pancreatic cancer population
   Hypothesis 3a: Education level, race, disease treatment stage are significant predictors of uncertainty and of health literacy in pancreatic cancer patients – Multiple linear regression will be performed to determine if these variables are significant predictors for uncertainty and multivariate regression will be also be performed to assess if they are significant predictors for health literacy as well. The anticipated results will be that education level, race, and disease treatment stage will be significant predictors for both health literacy and uncertainty.
   Hypothesis 3b: **Age and sex are not significant predictors of uncertainty or of health literacy in pancreatic cancer patients** - Multivariate regression will be performed to determine if age and sex are significant predictors for uncertainty and multivariate regression will be also be performed assess if they are significant predictors for health literacy as well. The anticipated results will be that neither age not sex will come out as significant predictors for either uncertainty or health literacy.

6.0 Informed Consent Process

Participants 18 years of age and older will be consented in the clinic during scheduled visits. They will be consented by the study PI or by authorized, trained research personnel

listed on the Delegation of Authority. This study has minimal risks and does not provide treatment.

Patients will be given the opportunity to review study documents and ask questions, and will be given time to consider their participation prior to signing the consent. This study is limited to English-speaking patients, due to the instruments only being available in English, therefore, patients who are unable to read, write, and understand English will not be consented to this study.

The investigator will acknowledge the patient's valuable contribution in participating in the study and explain the long-term goal of assessing the needs of pancreatic cancer patients to help clinicians enhance their communication skills and improve the way they engage patients in health care decisions.

7.0 Data Confidentiality:

The questionnaires will not contain identification information but only a participant number. Data will only be available to the PI and research team members directly involved with the collection and analysis of data related to this project. IRB approval will be obtained for any exchange of data outside of MD Anderson.

The members of the research team will be trained to maintain any patient health information confidential. Training will be documented as required by institutional policy.

Data Storage: The questionnaires will not contain identification information but only a participant number. The information key linking the participant number to his or her identification will be kept separate and secure. The PI and research staff will minimize risk by only storing information containing subject identifiers in locked file storage, on password-protected computers, and/or in a password protected database. In addition, access to patient identifiers will be limited to the minimum number of necessary research personnel, and only to those research personnel directly involved with obtaining patient information. Keys containing information linking study subjects to personal identifiers will be maintained in locked storage for paper records or behind institutionally approved firewall and electronic security measures for electronic keys, and available ONLY to the PI and research personnel. Information containing subject personal identifiers will not be removed from MD Anderson Cancer Center and will not be shared in publications or reports concerning this research study.

Data Sharing: Study data will not be shared with any individuals or entities that are not involved in the study. De-identified data may be shared with IRB-approved collaborating sites (PI's UT-Health Science Center Dissertation Committee). Sharing of data will be done only by secured mechanisms, as approved by MD Anderson Information Security.

Final disposition of study records: These data will be used only for this research study. Data that is in hard-copy form will be retained on site until the study is terminated, and may be stored indefinitely, per institutional standards, in long-term off-site storage with

an MD Anderson approved, secured contract site. Electronic data will be retained indefinitely on MD Anderson servers behind the institutional firewall. Data will not be shared with any party outside of MD Anderson and will not be retained or disseminated for other research without prior IRB approval.

8.0 Distress Plan

Participants will be provided information on the benefits, and the importance of knowledge gained from the study. The voluntary nature of the study will be emphasized and it will be explained to patients and clinicians that declination of participation in the study will not affect clinical treatment and/or care.
The Uncertainty in Illness Theory by Mishel defines uncertainty as a cognitive state wherein there is inability to assign value or meaning to illness-related events. Although Mishel conceptualized and designed the MUIS-C to measure a cognitive state and included no questions that address emotional distress, it is recognized that studes in a cancer population could be have associated distress. Since the MUIS-C manual does not delineate categories for low/moderate/high levels of uncertainty and because we do not know the levels of uncertainty in this population as it has not been previously studied, we cannot use the MUIS-C score to judge low-med-high uncertainty and assign a score that will prompt implementation of a distress plan. We will observe the patient for signs of unease or discomfort with the study and also review the responses so that items with answers that state "strongly agree" or for reservely scored items, those with "strongly disagree" will be reported to the clinical team so that the patient's uncertainty over their disease and management can be addressed.

The clinical team will also be notified if the patient verbalizes distress so that referral for counseling, supportive care, or psychiatry consult can be intiated. The patient will be informed that he/she may discontinue participation in the study at any time.

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Appendix E

Protocol Informed Consent Form

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent
Date of Consent Activation: 05/22/2017

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Uncertainty and Health Literacy In Pancreatic Cancer Patients
2017-0011

Study Chair: Rae Brana Reynolds

REYNOLDS, RAE BRANA — Participant's Name
639603 — Medical Record Number

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

1. DESCRIPTION OF STUDY

The goal of this research study is to learn how much pancreatic cancer patients understand about pancreatic cancer and the care that they are receiving for it.

This is an investigational study. There will be no cost to you for taking part in this study.

Up to 91 participants will be enrolled in this study. All will take part at MD Anderson.

2. STUDY PROCEDURES

If you agree to take part in this study, you will complete 2 questionnaires during an already scheduled clinic visit. One questionnaire will ask about health literacy (for example, how well you are able to read prescription labels and your understanding of medical terms and procedures) and the other questionnaire will ask about how you are feeling and if you understood the information told to you about your health and treatment.

The questionnaires will take about 20 minutes to complete. The total study time

including informed consent will take about 40 minutes.

Your medical record will also be reviewed for eligibility.

Length of Study Participation
Your participation in this study will be over after you have completed the questionnaires.

3. POSSIBLE RISKS

You should discuss the risks of **questionnaires** with the study chair. The known risks are listed in this form, but they will vary from person to person. Some questions may make you feel upset or uncomfortable. You may refuse to answer any question. If you have concerns after completing the questionnaire(s), you are encouraged to contact your doctor or the study chair.

If you are experiencing distress related to your illness or care, please let the researchers know. They will also notify your personal doctors if any of your responses to the questionnaires suggest you may want additional support about your care or illness.

Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study. There will be no personal identifying information connected to your questionnaire answers.

This study may involve unpredictable risks to the participants.

4. POTENTIAL BENEFITS

Future patients may benefit from what is learned. There are no benefits for you in this study.

5. OTHER PROCEDURES OR TREATMENT OPTIONS

You may choose not to participate in this study.

6. STUDY COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (health maintenance organization [HMO], health insurance company, etc.), will be your responsibility.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

ADDITIONAL INFORMATION

7. You may ask the study chair (Rae Brana Reynolds, at 713-792-6940) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB – a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.

8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you withdraw from this study, you can still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair or the IRB of MD Anderson.

10. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

11. MD Anderson may benefit from your participation and/or what is learned in this study.

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s).

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson may be collecting and using your PHI. For legal, ethical, research, and safety-related reasons, the research team may share your PHI with:

- The OHRP
- The IRB and officials of MD Anderson
- Dr. Terri Armstrong – NIH, Dr. Nikhail Padhye – UT Houston and Dr. Geraldine Wood - UT Houston
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

B. Signing this consent and authorization form is optional but you cannot take part in this study if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible according to state and federal law. However, in some situations, health authorities could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, the data collected up to that point can be used and included in data analysis, but no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT/AUTHORIZATION

Having read and understood the above and having had the chance to ask questions about this study, think about the study, and talk with others as needed, I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ Date/Time: _____

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ Date/Time: _____

ASSENT OF MINOR
The participant is not under the age of 18

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)
A legally authorized representative did not sign this consent on behalf of the patient.

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under this protocol.

_____ Date/Time: _____

Appendix F

Mishel Uncertainty in Illness Scale-Community

MISHEL UNCERTAINTY IN ILLNESS SCALE – COMMUNITY FORM

INSTRUCTIONS:

Please read each statement. Take your time and think about what each statement says. Then place a "X" under the column that most closely measures how you are feeling TODAY. If you agree with a statement, then you would mark under either "Strongly Agree" or "Agree". If you disagree with a statement, then mark under either "Strongly Disagree" or "Disagree". If you are undecided about how you feel, then mark under "Undecided" for that statement. Please respond to every statement.

1. **I don't know what is wrong with me.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

2. **I have a lot of questions without answers.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

3. **I am unsure if my illness is getting better or worse.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

4. **It is unclear how bad my pain will be.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

5. **The explanations they give about my condition seem hazy to me.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

6. **The purpose of each treatment is clear to me.(reverse scoring)**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

7. **My symptoms continue to change unpredictably.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

8. **I understand everything explained to me.(reverse scoring)**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

9. **The doctors say things to me that could have many meanings.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

10. **My treatment is too complex to figure out.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

11. **It is difficult to know if the treatments or medications I am getting are helping.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

12. **Because of the unpredictability of my illness, I cannot plan for the future.**

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

13. The course of my illness keeps changing. I have good and bad days.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

14. I have been given many differing opinions about what is wrong with me.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

15. It is not clear what is going to happen to me.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

16. The results of my tests are inconsistent.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

17. The effectiveness of the treatment is undetermined.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

18. Because of the treatment, what I can do and cannot do keeps changing.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

19. I'm certain they will not find anything else wrong with me.(reverse scoring)

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

20. The treatment I am receiving has a known probability of success. (reverse scoring)

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

21. They have not given me a specific diagnosis.

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

22. The seriousness of my illness has been determined.(reverse scoring)

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

23. The doctors and nurses use everyday language so I can understand what they are saying.(reverse scoring)

Strongly Agree (5)	Agree (4)	Undecided (3)	Disagree (2)	Strongly Disagree (1)
_____	_____	_____	_____	_____

Appendix G

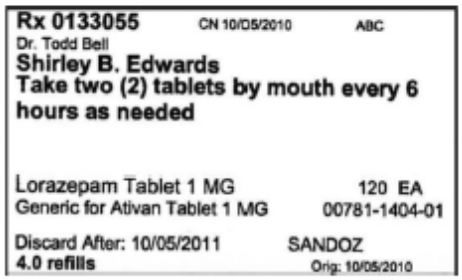
Cancer Health Literacy Test - 30

Participant ID #: _____

Cancer Health Literacy Test (CHLT- 30)

1) Doctors often recommend high calorie and high protein foods for cancer patients in treatment. Which is the highest in calories and protein?
   a. French fries
   b. Cheeseburger
   c. Hard-boiled egg

2)



Shirley took two Lorazepam at 2 p.m. What time can she take the next dose?
   a. 6 p.m.
   b. 7 p.m.
   c. 8 p.m.

3) Adjuvant therapy is cancer treatment generally given after a tumor is removed. Neo-adjuvant therapy is cancer treatment generally given to shrink a tumor before surgery.
   Mr. Davis has had his tumor surgically removed. After his surgery, he will get chemotherapy. The chemotherapy is:
   a. Neo-adjuvant
   b. Adjuvant

4) The normal range for hemoglobin for a male is 13.3–17.2 g/dl. Joe's hemoglobin is 9.7 g/dl. Is Joe within the normal range?
   a. Yes
   b. No

Dumenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Participant ID #: _____

5) In people who develop oral cancers, 25% of these cases occur in the tongue. Oral cancer occurs in the tongue:
   a. 1 out of every 25 cases
   b. 25 out of every 100 cases
   c. 25 out of every 1000 cases

6) Possible side effects of Tamoxifen:
   More than 30% of patients experience
   - Hot flashes
   - Swelling
   - Vaginal discharge
   - Loss of libido

   10% to 29% of patients experience
   - Nausea
   - Menstrual irregularities
   - Mood changes
   - Weight loss

   Which side effect is more common for patients taking Tamoxifen?
   a. Swelling
   b. Weight Loss

7) Chemotherapy treatment A has a 92% success rate and a long-term complication rate of 15.5%. Treatment B has a 95.9% success rate and a long-term complication rate of 3.8%.
   Which treatment has a lower risk of long-term complications?
   a. Treatment A
   b. Treatment B

8) The purpose of palliative care is to cure cancer.
   a. True
   b. False

9) A biopsy of a tumor is done to:
   a. Remove it
   b. Diagnose it

Dumenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Participant ID #: _____

c. Treat it

10)

Appointment Card

Mammogram/Chest X-ray: _____

- ☐ Purple Clinic, 3rd Floor
- ☐ Yellow Clinic Radiology
- ☐ Green Hospital, 3rd Floor

CT Scan/MRI/Interventional Radiology : Tuesday 05/15 12pm

Please arrive __30__ *minutes/hour(s) early*

Nothing to eat or drink _2_____ *hour(s) prior to test/procedure*

- ☐ Purple Clinic, 3rd Floor
- ☑ Yellow Clinic Radiology

Bone Scan, MUGA: _____

Please arrive 30 minutes early

- ☐ Purple Clinic, 3rd Floor

Above is Maria's appointment card. Where should Maria go for her appointment?

a. Purple Clinic
b. Yellow Clinic
c. Green Hospital

11) Fever classifications:

- None to mild: temperature is 98.6°F to 100.4°F
- Moderate: temperature is 100.5°F to 104°F**
- Severe: temperature is greater than 104°F**

(**Call your doctor right away if you experience this.)

Pete has a temperature of 100.3°F. According to the chart, should he call his doctor?

a. Yes
b. No

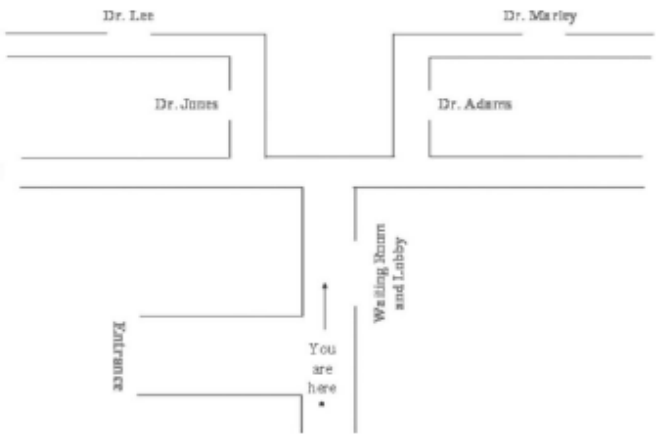
12) If a patient has stage 1 cancer, it means the cancer is:

a. Localized
b. In nearby organs
c. In distant sites

Dumenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Participant ID #: _____

13)



Ms. Rivera needs directions to get to her first appointment. The receptionist tells her to walk to the end of the hall and take a right turn, the first left turn, and then go to the first door on the left. If Ms. Rivera follows these directions, where will she end up?

a. Dr. Lee's Office
b. Dr. Marley's Office
c. Dr. Adams' Office

14) The degree to which a drug can have a beneficial effect is called:

a. Impotency
b. Efficacy
c. Dexterity

15) Exposing a tumor to air during surgery causes the tumor to spread.

a. True
b. False

16) Brand name drugs have the same active ingredients as generic drugs with a little extra that makes them better.

a. True
b. False

Dumenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Participant ID #: _____

17) The overall five-year survival rate for prostate cancer is 98%. This means that five years after treatment, 98% of prostate cancer patients will be expected to:
    a. Be alive
    b. Be cancer-free
    c. Die

18) An appointment card says not to eat or drink anything 9 hours prior to the appointment. Sally has an appointment at 11:15 a.m. on Friday. What time should she stop eating or drinking?
    a. Thursday at 11:15 p.m.
    b. Friday at 1:15 a.m.
    c. Friday at 2:15 a.m.

19) Scientists estimate that smoking is responsible for 85% to 90% of lung cancer deaths. This means that 85% to 90% of smokers will get lung cancer.
    a. True
    b. False

20) The role of a physical therapist is to talk to a patient about emotional needs.
    a. True
    b. False

21) A tumor is considered "inoperable" when it cannot be treated with:
    a. Radiation Therapy
    b. Surgery
    c. Chemotherapy

22) When receiving radiation, patients should eat foods that are high in fiber and avoid eating foods containing lots of spices, caffeine or dairy products. Which of the following foods is best to eat when receiving radiation?
    a. Curry
    b. Ice cream
    c. Bananas

Dumenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Participant ID #: _____

23) When a cancer has metastasized it means it has:

a. Spread to other parts of the body
b. Spread to other parts of the originally affected organ
c. Stopped spreading

24) A benign tumor is cancerous.

a. True
b. False

25) Sally will get radiation therapy once a day, Monday through Friday. If Sally has therapy for 4 weeks, how many times will she get radiation therapy?

a. 5
b. 15
c. 20

26) Of 100 people receiving treatment, half are expected to respond to the treatment. Of those who respond, half are expected to have complications. How many people who respond to treatment are expected to have complications?

a. 25
b. 35
c. 50

27) If patients get better by taking Medicine B twice a day, then if they take Medicine B 3 times a day, patients will get better faster.

a. True
b. False

Dumenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Participant ID #: _____

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Chapter 2 – Treatment options .....p. 52
Chapter 3 – Talking to others about your cancer .... p. 86

28) If Ms. Liu wants to learn more about the side effects of radiation, which chapter is most likely to have this information?

a. Chapter 1
b. Chapter 2
c. Chapter 3

29) Mrs. Bell takes her first pill at 10:00 a.m. If she takes this medicine every 4 hours, when would she need to take her third pill?

a. 2:00pm
b. 4:00 p.m.
c. 6:00 pm

30)

▲ RADIATION	ENDOSCOPY ▲
◀ ROOMS 200–300	ROOMS 100–200 ▶
◀ ROOMS 400–500	ROOMS 300–400 ▶

If Mr. Anthon needs to meet his doctor in room 202, which direction should he go?

a. Straight ahead
b. Right
c. Left

Dursenci, et al. (2014). Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun, 19 Suppl 2*, 205-224. doi: 10.1080/10810730.2014.943377

Appendix G

Demographic and Clinical Data Guide

MD Anderson Cancer Center

Making Cancer History®

STUDY DEMOGRAPHIC FORM

Participant ID Number:_____ **Participant Age in years:** _____

PHYSICIAN *(please check)*:

___ Dr. JASON FLEMING
___ Dr. JEFFREY E. LEE
___ OTHER _____
___ Dr. MATTHEW KATZ
___Dr. CHING-WEI TZENG

SEX *(please check)*:

___ MALE
___FEMALE

MARITAL STATUS *(please check)*:

___ MARRIED
___ SINGLE
___ OTHER
___WIDOWED
___MARRIED; CURRENTLY SEPARATED
___UNMARRIED WITH SIGNIFICANT OTHER

RACE/ETHNICITY *(please check)*:

___ ASIAN
___ AMERICAN INDIAN/ ALASKA NATIVE
___ BLACK/ AFRICAN AMERICAN
___ OTHER _____
___HISPANIC/LATINO
___NATIVE HAWAIIAN/PACIFIC ISLANDER
___WHITE /CAUCASIAN

EDUCATION STATUS *(please check)*:

___ SOME HIGH SCHOOL
___ COMPLETED HIGH SCHOOL
___ SOME COLLEGE
___ COMPLETED COLLEGE
___VOCATIONAL SCHOOL AFTER HIGH SCHOOL
___SOME GRADUATE SCHOOL AFTER COLLEGE
___COMPLETED GRADUATE DEGREE

PHASE OF TREATMENT *(please check)*:

___ BEFORE SURGERY
___ WITHIN 2 YEARS AFTER SURGERY
___WITHIN 5 YEARS AFTER SURGERY
___5 YEARS OR MORE AFTER SURGERY

WHICH OF THESE DEVICES DO YOU HAVE FOR PERSONAL USE:

____ MOBILE PHONE
____ MOBILE TABLET (ex: iPad/similar device)
____LAPTOP
____DESKTOP COMPUTER

DO YOU USE A SMART PHONE FOR ANYTHING OTHER THAN PHONE CALLS?

___ YES___NO

DO YOU CHECK YOUR MD ANDERSON LECTRONIC CHART FOR YOUR MEDICAL INFORMATION OR TEST RESULTS?

___ YES___NO

Appendix I

Human Subjects Research Training Certificates

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Certificate of Completion

Rae Reynolds (116252)

has successfully completed

FY16 EEE Direct Patient Care Manager/Faculty - Human Subjects Research

August 24, 2016

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Certificate of Completion

Rae Reynolds (116252)

has successfully completed

Human Subjects Protection Training Curriculum

April 28, 2015

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Certificate of Completion

Rae Reynolds (116252)

has successfully completed

HSPT: Informed Consent

April 28, 2015

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Certificate of Completion

Rae Reynolds (116252)

has successfully completed

HSPT: Regulations

April 28, 2015

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Certificate of Completion

Rae Reynolds (116252)

has successfully completed

HSPT: History & Ethics

April 28, 2015

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COURSEWORK REQUIREMENTS REPORT*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Rae Reynolds (ID: 5478183)
- **Email:** rae.zyn.b.reynolds@uth.tmc.edu
- **Institution Affiliation:** University of Texas Health Science Center at Houston (ID: 661)
- **Phone:** 7137945360

- **Curriculum Group:** Human Research
- **Course Learner Group:** Group 2 Social and Behavioral Researchers and Key Personnel
- **Stage:** Stage 1 - Basic Course

- **Report ID:** 19144217
- **Completion Date:** 04/05/2016
- **Expiration Date:** 04/05/2019
- **Minimum Passing:** 80
- **Reported Score*:** 100

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED
Avoiding Group Harms - U.S. Research Perspectives (ID: 14080)	03/29/16
Belmont Report and CITI Course Introduction (ID: 1127)	04/05/16
History and Ethical Principles - SBE (ID: 490)	04/05/16
Basic Institutional Review Board (IRB) Regulations and Review Process (ID: 2)	04/05/16
Informed Consent - SBE (ID: 504)	04/05/16
Records-Based Research (ID: 5)	04/05/16
Populations in Research Requiring Additional Considerations and/or Protections (ID: 16680)	04/05/16
Research with Children - SBE (ID: 507)	04/05/16
Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates (ID: 10)	04/05/16
Internet-Based Research - SBE (ID: 510)	04/05/16
Research and HIPAA Privacy Protections (ID: 14)	04/05/16
Conflicts of Interest in Research Involving Human Subjects (ID: 488)	04/05/16
University of Texas Health Science Center at Houston (ID: 1000)	04/05/16

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COURSEWORK REQUIREMENTS REPORT*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Rae Reynolds (ID: 5478183)
- **Email:** rae.zyn.b.reynolds@uth.tmc.edu
- **Institution Affiliation:** University of Texas Health Science Center at Houston (ID: 661)
- **Phone:** 7137945360

- **Curriculum Group:** Responsible Authorship and Publication
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - RCR

- **Report ID:** 19144220
- **Completion Date:** 03/29/2016
- **Expiration Date:** N/A
- **Minimum Passing:** 80
- **Reported Score*:** 100

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED
Authorship (RCR-Basic) (ID: 16597)	03/29/16

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COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COURSEWORK REQUIREMENTS REPORT*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Rae Reynolds (ID: 5478183)
- **Email:** rae.zyn.b.reynolds@uth.tmc.edu
- **Institution Affiliation:** University of Texas Health Science Center at Houston (ID: 661)
- **Phone:** 7137945360

- **Curriculum Group:** Conflicts of Interests in Research Training
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - RCR

- **Report ID:** 19144219
- **Completion Date:** 03/29/2016
- **Expiration Date:** N/A
- **Minimum Passing:** 80
- **Reported Score*:** 82

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED
Conflicts of Interests in Research Training (ID: 14415)	03/29/16

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TRANSLATING RESEARCH INTO PRACTICE

Section Editors: Jeannine M. Brant, Marilyn L. Haas-Haseman, Steven H. Wei, and Rita Wickham

Clinical Management of Pancreatic Cancer

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From University of Texas MD Anderson Cancer Center, Houston, Texas

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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J Adv Pract Oncol 2014;5:356–364

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States (American Cancer Society [ACS], 2014). In 2014, the ACS estimates 46,420 new cases of pancreatic cancer with 39,590 deaths in the United States. Unfortunately, 80% of patients diagnosed with pancreatic cancer present with metastatic or locoregional disease at initial diagnosis (Chatterjee et al., 2012a; Karmazanovsky, Fedorov, Kubyshkin, & Kotchatkov, 2005). Because metastatic and locally advanced extrapancreatic disease is an exclusion criterion for surgical treatment, this leaves only a minority of patients initially presenting with pancreatic cancer eligible for surgical resection (Chatterjee et al., 2012a).

The only treatment for pancreatic cancer with curative potential is resection of the involved portion of the pancreas, so with a small subgroup of patients presenting with resectable pancreatic cancer at initial diagnosis, the prognosis for this patient population is grim.

While the 5-year survival rates for many oncologic diseases have improved, the 5-year survival rate for pancreatic cancer remains dismal at 6% (ACS, 2014). Even at high-volume specialty centers, where the 5-year survival rate for patients is higher than in the general population, disease recurrence is still a major problem. For patients who have undergone surgical resection of the involved pancreas, published series from high-volume referral centers examining long-term survivors indicate that only 10% to 27% of patients with early-stage disease who underwent resection survived at least 5 years (Katz et al., 2009).

An MD Anderson Cancer Center (MDACC) analysis of 86 patients who received preoperative radiation and chemotherapy in the form of gemcitabine followed by resection reported that 11% of patients had local pancreatic disease recurrence after resection, 23% had liver metastasis after resection, and 59% had tumor recurrence with distant organ metastasis after resection (Evans et al., 2008).

Another MDACC study of 90 patients who received radiation and chemotherapy in the form of gemcitabine combined with cisplatin reported 25% of study patients presenting with local pancreatic disease recurrence after surgery and 73% of

patients had tumor recurrence with distant organ metastasis after surgery (Varadhachary et al., 2008). There is a high frequency of subclinical metastases at initial presentation as well as a high frequency of undetectable extrapancreatic disease at the time of surgical resection, which also contributes to the poor long-term outcomes (Chatterjee et al., 2012b).

RISK FACTORS

Although the exact mechanism of cause and effect has yet to be clearly elucidated, tobacco smoking is recognized as a strong risk factor for pancreatic cancer (Lochan, Reeves, Daly, & Charnley, 2011). Other risk factors such as alcohol consumption, chronic pancreatitis, and diabetes mellitus are often mentioned in the literature but require more epidemiologic studies and clinical research for further substantiation. Plasma 25-hydroxy vitamin D, also known as 25(OH)D, has been examined; among participants in five large prospective cohorts, higher plasma levels of 25(OH)D were associated with a lower risk for pancreatic cancer (Wolpin et al., 2012).

Genetics and a family history of disease are recognized risk factors for developing pancreatic cancer as well. Approximately 5% to 10% of patients with pancreatic cancer have a family history of the disease (Hidalgo, 2010). Individuals with the *BRCA2* mutation who are known to have an increased risk for developing breast and ovarian cancers are now recognized to have an increased risk for developing pancreatic adenocarcinoma (Moran et al., 2012). Other genes with variants associated with increased pancreatic cancer risk include *BRCA1, PALB2, ATM, CDKN2A, APC, MLH1, MSH2, MSH6, PMS2, PRSS1,* and *STK11* (Solomon, Das, Brand, & Whitcomb, 2012).

PRESENTING SIGNS AND SYMPTOMS

Pancreatic cancer will often develop without clear early signs or symptoms, and the eventual manifestations will depend on the tumor location within the gland. Up to 50% of pancreatic cancer patients will present with jaundice, which is more common with patients whose cancers are located in the head of the pancreas where tumors can cause obstruction of the adjacent biliary system (Bose, Katz, & Fleming, 2012). Figure 1 depicts a cancer in the head of the pancreas. Other common manifestations are vague abdominal discomfort, nausea, and weight loss. Large tumors that advance beyond the pancreas can also cause duodenal obstruction or gastrointestinal bleeding. Steatorrhea can also result from obstruction of the pancreatic duct, whereas hyperglycemia and diabetes have been associated with early manifestation of disease. Patients with advanced disease can also present with pain, ascites, and depression. Laboratory study abnormalities can include elevated liver function studies, hyperglycemia, and anemia (Hidalgo, 2010).

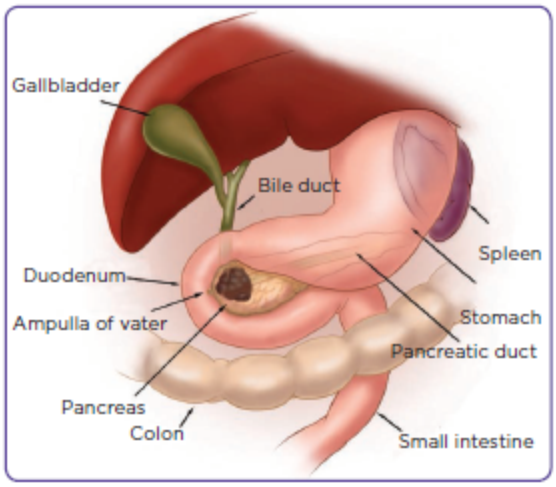

Figure 1. Pancreatic cancer: tumor in the pancreatic head. ©2008 The University of Texas MD Anderson Cancer Center.

SCREENING AND EARLY DETECTION

The relative lack of symptoms at the early stage of disease makes early diagnosis of pancreatic cancer rare. An additional detriment to early diagnosis is the lack of an established standard for screening or prevention, as there is no single reliable test for early detection of pancreatic cancer for the general population (Greenhalf, Grocock, Harcus, & Neoptolemos, 2009). The only screening programs that are currently available are in research settings and are narrowly focused on detecting potentially precancerous lesions among high-risk individuals (Shin & Canto, 2012).

The International Cancer of the Pancreas Screening (CAPS) Consortium summit on the man-

agement of patients with increased risk for familial pancreatic cancer reached a consensus that first-degree relatives of patients with pancreatic cancer from a kindred who has at least two affected first-degree relatives and patients with Peutz-Jeghers syndrome are candidates for screening (Canto et al., 2013). The consortium identified mutation carriers of *p16*, *BRCA2*, and hereditary nonpolyposis colorectal cancer with more than one affected first-degree relative as candidates for screening as well. There was no consensus on the age to initiate screening or stop surveillance, but it was agreed that initial screening should include endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography. There was also consensus that surgery, when recommended, should be performed at a high-volume center (Canto et al., 2013).

DIAGNOSIS

The goals of pancreatic cancer evaluation are to establish a tissue diagnosis of pancreatic cancer and to determine resectability as well as disease stage to help guide treatment planning. In addition to physical examination and a careful history assessment, pancreatic cancer evaluation includes laboratory, diagnostic radiology, and endoscopic studies. Biopsy for cytopathologic tissue diagnosis can be performed with radiology guidance or by endoscopic means (Hidalgo, 2010; Lee & Lee, 2014).

There is no known biomarker specific to pancreatic cancer, but carbohydrate 19-9 (CA 19-9) has demonstrated clinical value for therapeutic monitoring and for surveillance of disease recurrence in patients with a history of pancreatic cancer. It is important to note that CA 19-9 may be elevated during periods of cholestasis and that some patients with pancreatic cancer do not express elevations in CA 19-9, as there is a subgroup of about 10% who are unable to synthesize CA 19-9 and have undetectable levels, even in advanced stages of disease (Hidalgo, 2010).

The diagnostic radiology test of choice for initial pancreatic cancer evaluation is a multiphase, multidetector helical computed tomography (CT scan) with utilization of contrast material (Hidalgo, 2010). This test performed specifically with a pancreatic protocol provides essential details on the anatomic relationship of the tumor to adjacent organs and blood vessels, specifically the superior mesenteric vein, portal vein, superior mesenteric artery, celiac axis, and hepatic artery. A CT scan with contrast can correctly predict resectability in pancreatic cancer with 80% to 90% accuracy (Karmazanovsky et al., 2005). It also provides information on extrapancreatic lesions suspicious for metastatic disease. Positron emission tomography (PET) can be used to supplement CT scan findings during the evaluation and treatment phases.

Endoscopic procedures such as EUS with fine-needle aspiration and endoscopic retrograde cholangiopancreatography (ERCP) are commonly used for pancreatic cancer evaluation (Ross et al., 2008). An esophagogastroduodenoscopy (EGD) with EUS is useful in characterizing tumor details and obtaining tissue diagnosis. It can also be valuable in identifying a cancerous tumor that it is not clearly identifiable on a CT scan as it has better sensitivity for smaller pancreatic lesions (Ross et al., 2008). An ERCP is used for evaluation and management in patients with jaundice and cholestasis. It is used as a diagnostic tool to assess for a biliary stricture resulting from pancreatic cancer obstructing the bile duct and also as a guide in obtaining cytologic brushings of the area of the stricture for cytopathology studies (Hidalgo, 2010). In addition to its value as a diagnostic tool, it is also a therapeutic procedure that guides stent placement to relieve biliary tract compression by pancreatic cancer.

STAGING OF PANCREATIC CANCER

The tumor-node-metastasis (TNM) classification system issued by the American Joint Committee on Cancer (AJCC) is used to stage pancreatic cancer. The size of the tumor and its relationship to vital blood vessels are taken into account when categorizing the tumor from TX to T4. The extent of regional lymph node involvement defines nodal classification ranging from NX to N1, whereas the presence and/or absence of identifiable metastasis to distant organs designates the metastatic category as M0 or M1, respectively. Table 1 presents details of the levels that comprise each component of the TNM taxonomy, while Table 2 summarizes the AJCC staging system for pancreatic cancer using groupings categorized according to the TNM classification.

The AJCC staging system has prognostic value but cannot consistently direct clinical manage-

Table 1. TNM Classification for Pancreatic Cancer[a]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery; unresectable primary tumor
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Note. Adapted from National Cancer Institute (2014).
[a]American Joint Committee on Cancer staging system.

Table 2. TNM Staging of Pancreatic Cancer[a]

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2, T3	N1	M0
III	T4	N0 or N1	M0
IV	T1, T2, T3, T4	N0 or N1	M1

Note. Adapted from National Cancer Institute (2014).
[a]American Joint Committee on Cancer staging system.

ment because it requires information that is not always readily available during the initial phase of treatment planning. For example, in most cases, regional lymph node involvement is unknown until after the patient has undergone surgical resection. As such, the primary guide to clinical management of pancreatic cancer at initial diagnosis becomes the patient's eligibility for surgical resection rather than the TNM staging status. Different clinical staging systems have been developed to categorize pancreatic cancer according to surgical resectability, and these clinical staging systems help steer treatment planning for patients. The MDACC classifies pancreatic cancer as resectable, borderline resectable, locally advanced, and metastatic.

Resectable disease is characterized by the absence of extrapancreatic disease; a patent superior mesenteric vein-portal vein (SMV-PV) confluence; and clear tissue planes between the celiac axis (CA), superior mesenteric artery (SMA), and the common hepatic artery (Bose et al., 2012). At our institution, MDACC, *borderline resectable disease* is characterized by the absence of extrapancreatic disease and the presence of tumor involvement or occlusion of the SMV-PV confluence that is amenable to resection and reconstruction, tumor abutment of the SMA for less than 180° of its circumference, and short segment encasement of the hepatic artery (Bose et al., 2012).

Locally advanced disease is characterized by the presence of tumor encasement of the SMA or CA for greater than 180° of its circumference in the absence of extrapancreatic disease (Bose et al., 2012). Table 3 summarizes the criteria for these three clinical staging categories used for determination of resectability, and Figures 2, 3, and 4 provide illustrations of the different categories. In addition to these three, there is the category of *metastatic disease,* which is characterized by radiographic or clinical evidence of pancreatic cancer that has spread to distant organs or the peritoneum.

TREATMENT

Treatment and clinical management of pancreatic cancer are often determined by the clinical stage of the patient's disease and are usually focused on the question of disease resectability. Patients who have resectable disease are eligible for surgery and thus have a significantly improved prospect for long-term survival and cure. Chemotherapy, radiation, and surgery are utilized in the treatment of pancreatic cancer; the modalities utilized as well as the sequence in which they are administered often depend on the clinical stage of disease.

Table 3. MD Anderson Cancer Center Clinical/ Radiologic Staging of Pancreatic Cancer

Resectable
• No encasement of CA or SMA
• Patent SMV-PV confluence
• No metastatic disease
Borderline resectable
• SMV-PV occlusion with anatomy sufficient for venous reconstruction
• Short segment abutment of SMA
• Short segment abutment or encasement of HA
Locally advanced
• Encasement of SMA or CA

Note. CA = celiac axis; SMA = superior mesenteric artery; SMV = superior mesenteric vein; PV = portal vein; HA = hepatic artery. Adapted from Bose et al. (2012).

Resectable Pancreatic Cancer

For resectable pancreatic cancer, the primary recommendation from the National Comprehensive Cancer Network (NCCN) is to proceed immediately to surgical resection followed by adjuvant chemotherapy. However, there is also expert consensus and phase II clinical trial data that support the delivery of neoadjuvant therapy (i.e., chemotherapy and radiation administered prior to surgical resection) in selected patients with biopsy confirmation of adenocarcinoma (Halperin & Varadhachary, 2014).

The primary chemotherapeutic agents that have shown benefit in patients with pancreatic cancer are gemcitabine and fluorouracil (5-FU). The use of gemcitabine has shown an increased median disease-free survival to 13.4 months compared with 6.7 months in an observation group (Oettle et al., 2007). A 5-year actuarial survival of 21% was seen in patients treated with adjuvant 5-FU compared with 9% in patients randomized to receive nonadjuvant treatment (Halperin & Varadhachary, 2014).

There is conflicting information on the role of radiation in patients with resectable pancreatic cancer. A 2004 study confirmed that patients may benefit from adjuvant chemotherapy but showed a lower survival rate among patients treated with adjuvant chemotherapy combined with radiation when compared with patients who did not receive adjuvant chemotherapy and radiation (Neoptolemos et al., 2004). These results are in contrast to findings of multiple trials that have suggested a survival benefit in pancreatic cancer patients treated with radiation (Corsini et al., 2008; Herman et al., 2008; Hsu et al., 2010).

For patients with resectable pancreatic cancer, the delivery of neoadjuvant therapy is advocated by some centers, as it allows for early treatment of systemic disease in a population of patients widely believed to have micrometastasis at presentation (Evans et al., 2008). Additionally, it allows for identification of patients with rapidly metastatic disease and spares them from major operation unlikely to provide durable cure because of highly aggressive tumor biology. Moreover, delivery of neoadjuvant chemotherapy and radiation is posited to increase the rate of margin-negative resection (R0 resection) and reduce the risk of local disease recurrence (Evans et al., 2008).

Achieving microscopically negative surgical margins of resection is the goal of any pancreatic cancer operation (Evans et al., 2009). Surgical resection of pancreatic cancer is performed for patients whose radiographic imaging studies indicate resectable disease and whose clinical performance status is appropriate for surgery. The majority of pancreatic cancers arise in the area of the pancreatic head, and these lesions, if resectable, are treated with a pancreaticoduodenectomy. Pancreatic cancers located in the area of the pancreatic tail, if resectable, are treated with a distal pancreatectomy, which typically also involves a splenectomy depending on the splenic vessel involvement of the tumor.

A pancreaticoduodenectomy is commonly referred to as the Whipple procedure and involves the resection of the pancreatic head, duodenum, gallbladder, and a portion of the stomach (Figure 5). Reconstruction is then performed with a pancreaticojejunostomy, choledochojejunostomy, and duodenojejunostomy or gastrojejunostomy (Figure 6). A pancreaticoduodenectomy for resectable pancreatic cancer can be performed with pylorus preservation, especially in patients with a high risk for postoperative nutritional compromise. However, it is not typically performed in patients with bulky pancreatic head tumors that involve adjacent organs or in the presence of grossly positive pyloric or peripyloric lymph nodes (Bose et al., 2012).

Involvement of the SMV-PV is not considered an absolute contraindication to resection of pancre-

atic cancers at our institution. In 84% of patients, imaging studies can accurately predict the need for resection and reconstruction of the SMV-PV due to tumor involvement (Bose et al., 2012). Resection and reconstruction of the SMV-PV have been found to be safe. It has also been found that patients who require resection and reconstruction of the SMV-PV to achieve negative surgical margins have a similar overall survival rate as patients who undergo resection without the need for venous resection and reconstruction (Bose et al., 2012). At our institution, most patients with resectable pancreatic cancers who have venous involvement are treated preoperatively with chemotherapy and radiation. Expert consensus states that pancreaticoduodenectomy for pancreatic adenocarcinoma should be performed at high-volume institutions capable of and experienced in resection and reconstruction of major mesenteric veins (Evans et al., 2009).

Borderline Resectable Pancreatic Cancer

Because this category is relatively new and does not yet have a standard definition among institutions and organizations with expertise in pancreatic cancer management, standard treatment for borderline resectable disease is not well established; however, expert consensus statements were published in 2009 on the surgical treatment and combined-modality treatment of resectable and borderline resectable pancreatic cancers (Abrams et al., 2009; Evans et al., 2009)

Heterogeneity in the definitions as well as the interventions used by different institutions that have conducted studies on patients with borderline resectable disease remains. Multiple trials support the delivery of preoperative neoadjuvant therapy either with chemotherapy alone or in combination with radiation, including the use of FOLFIRINOX, which is a combination of 5-FU, oxaliplatin, irinotecan, and leucovorin followed by chemoradiation (Christians et al., 2014). However, there is no consensus standard on which chemotherapy or chemoradiation regimen in particular should be delivered prior to resection (Halperin & Varadhachary, 2014).

Unresectable Pancreatic Cancer

Locally advanced and metastatic pancreatic cancers are considered unresectable. Because resection of the involved pancreas is the only treatment that offers cure, unresectable disease is therefore considered incurable. In these palliative settings, there is no role for resection, and treatment usually consists of systemic chemotherapy and in some cases with chemoradiation. The role of radiation in combination with chemotherapy for locally advanced disease has been studied: Although chemoradiation has shown benefit, there has also been a noted increase in toxicity. The added morbidity and the low enrollment in clinical trials designed to examine its benefit have precluded a firm conclusion on its status as recommended treatment (Hidalgo, 2010).

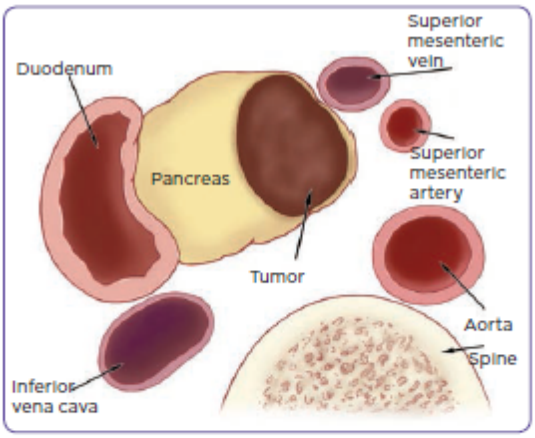

Figure 2. Resectable pancreatic cancer. ©2008 The University of Texas MD Anderson Cancer Center.

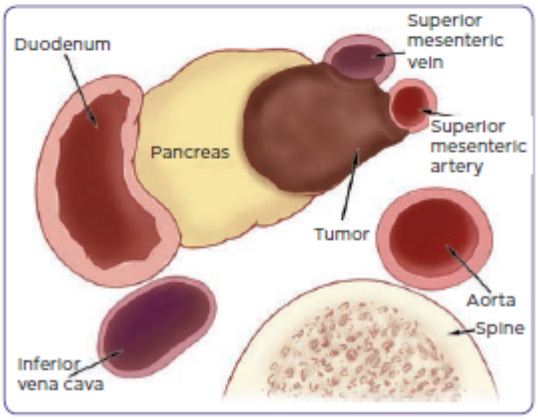

Figure 3. Borderline resectable pancreatic cancer. ©2008 The University of Texas MD Anderson Cancer Center.

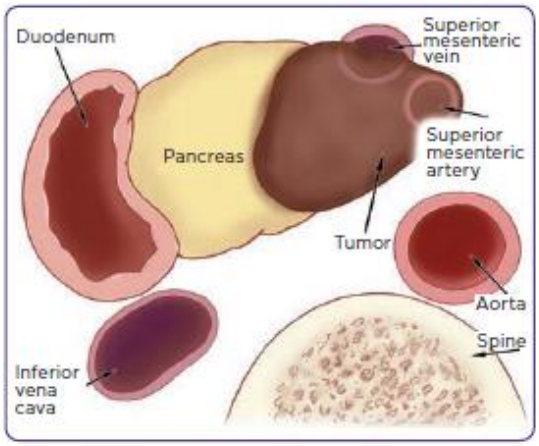

Figure 4. Locally advanced pancreatic cancer. ©2008 The University of Texas MD Anderson Cancer Center.

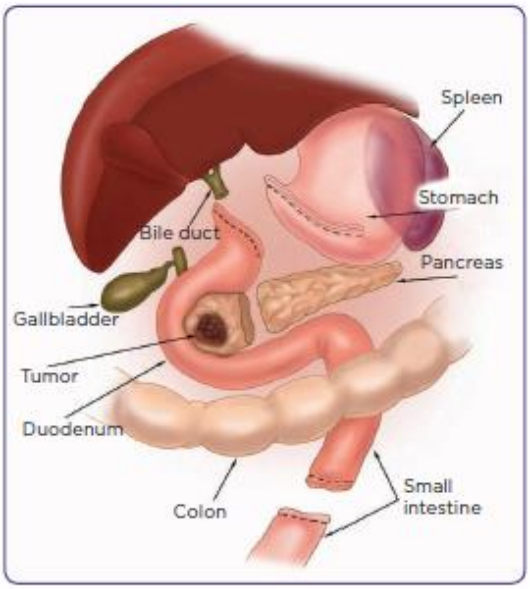

Figure 5. Pancreaticoduodenectomy: resection of distal stomach, bile duct, gallbladder, duodenum, head of the pancreas. ©2008 The University of Texas MD Anderson Cancer Center.

For systemic chemotherapy agents, gemcitabine has long been considered the treatment of choice for unresectable and metastatic pancreatic cancers. It has been used as a single agent and also in combination with other agents for treatment of advanced disease (Hidalgo, 2010). In a study published in 2011, FOLFIRINOX was shown to offer a survival advantage but increased toxicity compared with gemcitabine in patients with advanced disease (Conroy et al., 2011). As such, FOLFIRINOX has become an option for patients with metastatic disease, provided that they have an otherwise good performance status.

One randomized phase III study found that weekly gemcitabine combined with albumin-bound paclitaxel had a statistically significant prolongation of median overall survival in patients with metastatic pancreatic cancer when compared with single-agent gemcitabine (Von Hoff et al., 2013). This multinational, multi-institutional study of 861 patients yielded a median overall survival of 8.5 months for patients treated with albumin-bound paclitaxel combined with gemcitabine compared with 6.7 months for patients treated with gemcitabine alone. The patient group treated with combination therapy had a 1-year survival rate of 35% compared with 22% for the group that received single-agent gemcitabine; the 2-year survival rate was 9% for the group that received combination therapy and 4% for the group that received gemcitabine alone (Von Hoff et al., 2013).

SURVEILLANCE

At the MDACC, patients undergo posttreatment surveillance every 4 months for the first 2 years following completion of pancreatic cancer treatment; the visits are spread out to every 6 months after 2 years (Bose et al., 2012). The visits consist of a physical examination and surveillance tests including CT scan, serum CA 19-9, and chest x-ray. After 5 years, surveillance visits are scheduled on an annual basis (Bose et al., 2012).

FUTURE DIRECTIONS

Patients with pancreatic cancer encounter challenges throughout the different phases of their illness. Although some advances have been made in the evaluation and treatment of these patients, the poor prognosis associated with this disease underscores the need for continued efforts to enhance understanding of the underlying disease biology to promote progress in finding effective treatments. ●

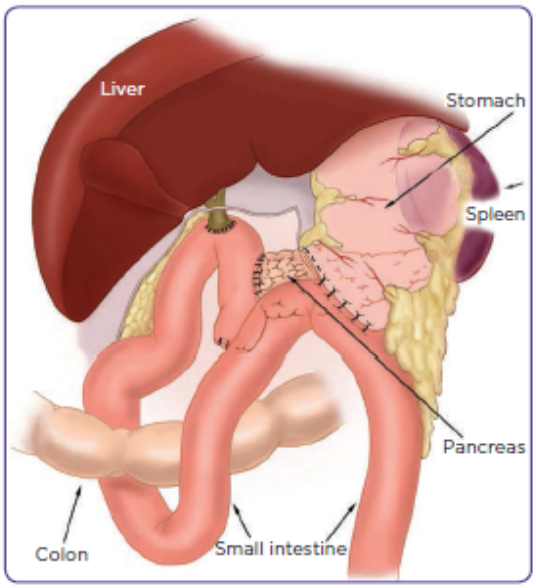

Figure 6. Pancreaticoduodenectomy: post-resection anastomoses. ©2008 The University of Texas MD Anderson Cancer Center.

Disclosure

The authors have no potential conflicts of interest to disclose.

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Section Editors: Jeannine M. Brant, Marilyn L. Haas-Haseman, Steven H. Wei, and Rita Wickham

Use of Radiographic Criteria to Predict Outcomes Following Surgery for Pancreatic Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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J Adv Pract Oncol 2014;5:365-370

Surgical resection of the pancreas is the only treatment for pancreatic cancer that offers curative potential. Because other treatment modalities such as chemotherapy and radiation only offer palliation, surgical resectability is critical, as it dictates the treatment plan and ultimately serves as a determinant for long-term survival. Unfortunately, 80% of patients diagnosed with pancreatic cancer present with metastatic or locoregional disease at initial diagnosis (Chatterjee et al., 2012; Karmazanovsky, Fedorov, Kubyshkin, & Kotchatkov, 2005). These patients are therefore deemed ineligible for resection at initial diagnosis given that metastatic and locally advanced extrapancreatic disease are exclusion criteria for surgical treatment.

As such, pancreatic cancer has a grim prognosis, with an overall survival rate of only 6% (American Cancer Society, 2014). According to Hidalgo (2010), patients with earlier stages of disease deemed resectable have higher median survival rates (stage IA, 24.1 months; stage IB, 20.6 months; stage IIA, 15.4 months; stage IIB, 12.7 months) compared with patients with advanced stages of disease considered to be unresectable (stage III, 10.6 months; stage IV, 4.5 months). The implications for long-term survival accentuate the importance of identifying characteristics that distinguish resectable from unresectable disease at the outset of diagnosis and treatment planning.

The involvement of the superior mesenteric vein (SMV) or the portal vein (PV) by pancreatic cancer was historically considered a contraindication for surgical resection (Katz, Fleming, Pisters, Lee, & Evans, 2008). These vessels are adjacent to the pancreas and are at high risk for involvement by the pancreatic tumor.

There remains concern that resection and reconstruction of the involved SMV-PV during pancreatic cancer surgery is a high-risk procedure given the higher than usual risk for perioperative complications owing to the additional complexity of surgery. Additionally, it is thought that these patients are also at high risk for early systemic failure due to the advanced nature of the primary tumor, and at high risk for margin-positive resection with surgery alone. However, in centers where experi-

enced surgical oncologists are performing a high volume of pancreatic cancer operations in a multidisciplinary setting, surgical outcomes have alleviated this concern (Evans et al., 2009). The quality of surgical resection affects long-term survival, and patients who undergo pancreatic cancer resection in high-volume hospitals with superior surgical oncologic expertise have higher survival rates than patients who undergo resection at low-volume centers, where surgical margins have been found to have a higher likelihood of being positive for residual disease (Bilimoria et al., 2008; Herman et al., 2008).

A 2012 study that examined hospital surgery volume, postoperative margin status, and long-term survival after pancreatic cancer resection found that high-volume hospitals were associated with significantly more cases of operative margins that were free from cancer (La Torre et al., 2012). The same study found that pancreatic resections at low-volume centers resulted in inferior operative margin outcomes and overall 5-year survival rate of patients (La Torre et al., 2012). In high-volume settings, there is more experience with safe and effective resection and reconstruction of the involved SMV and/or PV at the time of pancreatic cancer surgery, resulting in complete removal of the pancreatic tumor with R0/R1 outcomes. Hence, it is important to examine ways to develop standards in characterizing the tumor-vein interface (TVI) so that uniformity is established in discriminating between tumors that are potentially resectable or otherwise. The Table summarizes surgical margin clearance information referenced in this article.

REVIEW OF THE 2014 TRAN CAO ET AL. ARTICLE

Pancreatic cancer can present anywhere along the spectrum of resectable, borderline resectable, locally advanced, and unresectable disease. The article by Tran Cao et al. focuses on the borderline resectable category of tumors (Tran Cao et al., 2014). Borderline resectable disease has been categorized by the MD Anderson Cancer Center Pancreas Group according to three categories. Category A consists of disease that is questionable in terms of resection secondary to anatomic constraints. The level of vascular involvement is classified according to three conditions: tumor abutment (≤ 180°) of the SMA or celiac axis; tumor abutment or encasement (> 180°) of the circumference of the vessel of a short segment of the hepatic artery, usually at the origin of the gastroduodenal artery; short segment occlusion of the SMV, PV or SMV-PV confluence that is amenable to vascular resection and reconstruction because of patent venous access above and below the area of tumor-related occlusion. Category B centers on the concern for tumor biology, more specifically the notion of metastatic disease. Category C centers on each patient's performance status and their tolerance for major abdominal surgery.

Within the borderline A cohort of patients, accurate classification of the extent of disease is critical in determining the eligibility for surgery. The goal of a complete margin-negative resection (R0) is significant to long-term survival, as several studies have suggested similar survival rates for margin-positive surgery when compared with survival rates for unresectable local-regional disease or locally advanced disease (Jemal et al., 2007; Alexakis et al., 2004; Sener, Fremgen, Menck, & Winchester, 1999).

The surgical oncology group at the University of Texas MD Anderson Cancer Center (MDACC) has established that in a highly select patient population, an R0 margin resection can be achieved through the addition of vein resection. It was done with low perioperative morbidity, and survival rates were comparable to those of patients who underwent an R0 resection without venous resection. Furthermore, it was achieved with a complication rate of 22%, a mortality rate of 1.6%, and a median survival of 22 months (Bold et al., 1999). Venous resection should be strongly considered if it yields a margin-negative resection (R0) since survival is improved when compared with a microscopic (R1) or macroscopic (R2) resection (Bold et al., 1999; Harrison & Brennan, 1998).

Table. Resection Margin Classification

Status	Description
R0	Margin-negative resection
R1	Microscopic residual disease present at resection margin
R2	Gross; macroscopic residual disease present at resection margin

Note. Information from Evans et al. (2009).

METHODS

This article summarized a study designed to assess the ability of radiographic criteria to predict the need for SMV-PV resection and the presence of histologic vein invasion. A system to categorize the TVI based on the pancreatic tumor's relationship with the SMV-PV according to preoperative imaging was described, and its ability to accurately predict the need for venous resection and histologic vein involvement was evaluated. The study was conducted at the authors' institution, MDACC, and examined all patients who underwent pancreaticoduodenectomy from 2004 to 2011 for pancreatic adenocarcinoma originating in the pancreatic head. Clinical data on these patients were retrieved from the pancreatic tumor database maintained by the institution's pancreatic cancer surgery program within the Department of Surgical Oncology. Patients who did not undergo a preoperative multidetector computed tomography (CT scan) performed according to MDACC's diagnostic imaging department pancreatic protocol within 3 months before pancreaticoduodenectomy were excluded from analysis.

Additionally, patients whose final surgical pathology report indicated pancreatic adenocarcinoma arising from an intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN) were excluded from the study as well. By these criteria, 11 patients who did not undergo preoperative CT scan per the institution's pancreatic protocol within 3 months of pancreaticoduodenectomy, and 12 patients with final pathology demonstrating precursor IPMN or MCN lesions were excluded. Thus, 254 of 277 patients were eligible for the final analysis.

The pancreas protocol CT utilized consisted of images in two phases after injection of contrast, with positive or negative oral contrast as chosen by the protocoling radiologist. Bolus triggering was used to track the contrast in the vessels while it was injected into the patient to obtain images at the correct phases. Both phases were obtained at 2.5-mm slice thickness and reconstructed to 1.25- or 0.625-mm slice thickness. The images from the first phase were for analyzing the primary tumor, to identify variant arterial anatomy, and for assessing the relationship of the tumor to the arteries. The portal venous phase images were used to identify liver metastases and venous involvement. A dual-phase technique was used, as up to 40% of primary pancreatic tumors are of the same density of the pancreas and therefore essentially invisible (in the case of small operable cancers) on the later portal venous phase.

The preoperative pancreatic protocol CT scan of each eligible patient was reviewed by a single radiologist with expertise in gastrointestinal CT scan interpretation. The radiologist was blinded to each patient's clinical history. The circumferential TVI between the primary pancreatic tumor and the SMV-PV was measured on axial CT scan images and categorized as (1) *none*, when there was no direct contact between the pancreatic tumor and the vessels, as they were separated by normal pancreas or a fat plane; (2) *TVI < 180°*, when the pancreatic tumor had interface with the vein at less than 180° of the vein's circumference; (3) *TVI > 180°*, when there was interface of the pancreatic tumor with greater than 180° of the vessel's circumference; or (4) *vascular occlusion*, when there was occlusion of the vessel as evidenced by the absence of contrast within the lumen of the vein in association with the adjacent pancreatic tumor.

The requirement for SMV-PV resection during pancreaticoduodenectomy was determined by the operating surgeon during surgery based on the interface between the pancreatic tumor and the vein. SMV-PV resection was performed when the primary tumor was adherent to and not easily separated from the vein. Reconstruction of the vein was completed with primary closure or patch venoplasty when tangential resection was performed, whereas bypass graft with autologous internal jugular vein or bioprosthetic material was performed for segmental vein resection. The surgical specimen was then submitted for review, and the closest distance between the cancer cells and the margin where the superior mesenteric artery (SMA) was resected was measured microscopically. When applicable, the resected portion or segment of the SMV-PV was also submitted for review, evaluated for tumor involvement, and subsequently categorized as (1) no tumor involvement, (2) tumor invasion into the tunica adventitia, (3) tumor invasion into the tunica media or intima, or (4) tumor invasion into the SMV-PV lumen with or without thrombus. Patients who did not require or undergo SMV-PV resection during pan-

creaticoduodenectomy were considered to have no tumor involvement of the vein.

In addition to evaluating the ability of radiographic criteria to predict the need for venous resection, the presence of histologic invasion of the vein wall by tumor and the overall survival of patients who had and had not received chemoradiation prior to pancreaticoduodenectomy were also examined. In this study, patients treated with preoperative chemoradiation received three-dimensional, conformal radiation therapy of 30 Gy in 10 fractions or 50 Gy in 28 fractions with concomitant capecitabine, 5-fluorouracil, or gemcitabine. In some cases, gemcitabine-based chemotherapy was delivered prior to chemoradiation and subsequent pancreaticoduodenectomy.

ANALYSIS AND RESULTS

The investigators employed t-test and Pearson chi-squared analysis to assess differences in the clinical characteristics and demographics by TVI categories, venous resection, and final pathology results. Assessment of areas under the curve (AUC) was performed by constructing receiver operating characteristic (ROC) curves. These curves allowed the investigators to assess the ability of the TVI classification to accurately predict the intraoperative need for vein resection and the presence of vein invasion by tumor. Survival analysis was performed via the Kaplan-Meier method to estimate median survival for each clinical and demographic factor, and Cox regression analysis was used to identify hazard ratios for the variables under examination.

The CT scan review by the radiologist revealed that of the 254 patients eligible for review, the TVI breakdown consisted of 62 patients (24.4%) with no TVI, 154 patients (60.6%) with TVI ≤ 180°, 28 patients (11%) with TVI > 180°, and 10 patients (3.9%) with venous occlusion associated with the pancreatic tumor. SMV-PV resection was performed in 8 of the 62 patients (12.9%) who did not have TVI, 56 of the 154 (36.4%) with TVI ≤ 180°, 25 of the 28 (89%) with TVI > 180°, and 9 of the 10 (90%) with venous occlusion ($p < .001$). The rate of microscopically negative margins (R0 resection) was similar across TVI groups ($p = .25$), and microscopically negative margins were achieved in over 90% of resected cases, regardless of the preoperative TVI category.

Chemoradiation with or without induction chemotherapy was delivered to 194 patients (76.4%) prior to pancreaticoduodenectomy during which SMV-PV resection and reconstruction was performed in 98 patients (38.6%). Among these 98 patients, 93 had complete histopathologic assessment of the vein. The vein wall was invaded by cancer in 64 patients (68.8%), with 17 having involvement of the tunica adventitia, 42 having involvement of the tunica media/intima, and 5 having invaded the vein lumen. The investigators reported the clinical characteristics and outcomes for each TVI category and noted that primary cancers with greater circumferential TVI were larger, more likely to have been treated with preoperative chemoradiation, and more likely to have required resection of the SMV-PV during pancreaticoduodenectomy ($p < .001$).

An ROC curve was constructed to evaluate the ability of the preoperative TVI system to accurately predict whether SMV-PV resection would be necessary. The AUC of the ROC curve indicates how the TVI system can preoperatively discriminate between patients who require SMV-PV resection during pancreatic cancer extirpation and those who do not. The results showed an AUC of 0.734. An ROC curve was also constructed to evaluate the ability of the TVI system to accurately predict SMV-PV tumor invasion; this was calculated at 0.768. It represents the ability of the TVI system to discriminate preoperatively between patients whose postoperative histopathology will reveal tumor involvement of the SMV-PV and those whose will not. Given these results, the authors stated that the TVI achieved fair accuracy in predicting the need for venous resection and histopathologic vein invasion.

As for long-term outcomes, the investigators evaluated progression-free survival (PFS) and overall survival (OS). Pancreatic cancer surgery with SMV-PV resection and reconstruction was associated with a shorter median PFS (16.1 vs. 19.6 months; $p = .013$) and OS (27.8 vs. 44.5 months; $p = .002$) compared with surgery without SMV-PV resection. Additionally, the investigators also found that tumor vein involvement confirmed by histology was associated with a shorter median PFS (15.6 vs. 19.6 months; $p = .001$) and OS (27 vs. 40.4 months; $p = .001$) compared with absence of tumor vein involvement. Similarly, patients with a TVI > 180° had a shorter median PFS (15.9 vs 18.2 months;

$p = .006$) and OS (30.9 vs. 37.3 months; $p = .030$) than patients with TVI < 180°. Of note, patients who had no TVI were grouped with those who had a TVI < 180°, as the authors pointed out that the survival curves of these patients were similar.

LIMITATIONS AND STRENGTHS

The overall study has some limitations in that only the primary preoperative scan was reviewed, and the changes in TVI in response to preoperative neoadjuvant treatment were not examined. The authors acknowledged that it would have been useful to assess cases and note where tumor downstaging occurred. The study also excluded patients whose planned resections were aborted due to intraoperative findings.

Despite these acknowledged limitations, the authors pointed out the study's strengths, such as having one radiologist review the preoperative CT images for increased integrity in the uniform use of the TVI characterization system. All patients were also evaluated via a standardized, high-quality protocol specifically designed for pancreatic evaluation. In addition, the indications for surgical resection were also standardized, as were the surgical techniques and histopathologic evaluation of surgical specimens. The fact that evaluation and treatment occurred in a high-volume center experienced in the care of patients with borderline resectable disease was also noted as a fundamental strength of the study.

PRACTICAL IMPLICATIONS

Accurately characterizing pancreatic tumors is fundamental and critical for overall treatment planning. Concurrent vascular resection and reconstruction at the time of major pancreatic surgery has been, and continues to be, controversial due to the complexity of the surgical procedure itself, the limited experience of many surgeons regarding the described vascular work, and the potential for synergistic perioperative morbidity and mortality. Moreover, most pancreatic surgeons desire to minimize this perioperative risk given the aggressive nature of pancreatic adenocarcinoma, which has a known poor survival rate. Over the past 20 years, advances in pancreatic surgery have made it possible to resect and reconstruct the SMV-PV as well as the hepatic artery. This operation can be done safely and effectively as part of a pancreatectomy, when offered to the appropriate, well-selected patient population. The end result provides the potential for improved survival for such surgical patients.

Additionally, a multidisciplinary approach utilizing neoadjuvant chemotherapy and chemoradiation can facilitate the selection of patients whose tumors present favorable biology for such major operations. This neoadjuvant pathway is especially useful for localized tumors that are technically resectable but are at increased risk for R1 or R2 resection secondary to their close anatomic relationship to major vascular structures (Katz, Ahmad, & Nelson, 2013). Achieving a margin-negative (R0) resection is fundamental for the potential cure; the definition of borderline resectable pancreatic cancer and the proximity and involvement of major vascular structures often necessitates a combined resection and reconstruction of the SMV-PV region, in the absence of distant disease or disease involving structures that would preclude surgery (the SMA, celiac axis, and often the common hepatic artery; Kang, Hwang, Choi, & Lee, 2013). As previously outlined, the role for aggressive vascular resection and reconstruction is a critical aspect to facilitate complete tumor clearance, achieving an R0 resection for borderline resectable tumors.

The ability to standardize a preoperative classification system for describing TVI based on preoperative radiography is critical in determining resectability and in planning for pancreatic cancer surgery. It also has the potential to predict histopathologic information, with practical implications for assessing long-term survival. The system proposed by the authors is simple and does away with ambiguous terminology.

Although there is no widely accepted standard for classification of tumor at this time, it is valuable that experts are evaluating ways to establish uniformity to enhance the evaluation, treatment, and ongoing research efforts that benefit patients with pancreatic cancer. ●

Disclosure

The authors have no potential conflicts of interest to disclose.

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Review Article

The role of Advanced Practice Providers in interdisciplinary oncology care in the United States

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Contributions: (I) Conception and design: None; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Advanced Practice Registered Nurses (APRNs) and Physician Assistants (PAs), generally referred to as Advanced Practice Providers (APPs), are fundamental to interdisciplinary oncology care. As the projected demand for oncology services is anticipated to outpace the supply of oncologists, APPs will become increasingly vital in the delivery of oncology care and services. The training, education, and scope of practice for APPs gives the interdisciplinary care team professionals that deliver high-quality clinical services and provide valuable contributions and leadership to health care quality improvement initiatives. Optimizing the integration of APPs in oncology care offers immense advantages towards improvement of clinical outcomes.

Keywords: Nurse Practitioners (NPs); Physician Assistants (PAs); Advanced Practice Providers (APPs); interdisciplinary care

Submitted Apr 06, 2016. Accepted for publication May 09, 2016.
doi: 10.21037/cco.2016.05.01
View this article at: http://dx.doi.org/10.21037/cco.2016.05.01

Introduction

Advanced Practice Registered Nurses (APRNs) and Physicians Assistants (PAs) are essential to interdisciplinary care of oncology patients. Generally titled in the United States as Advanced Practice Providers (APPs), APRNs and PAs have continued to develop their practice patterns and enhance their roles in oncology care. With the ongoing health care reform, projected increase in cancer incidence (1), and predicted shortage of oncology physicians (2), APPs are increasingly valuable to interdisciplinary oncology care. According to the results of a study commissioned by the American Society for Clinical Oncology (ASCO) in 2007, the demand for oncology visits is expected to increase 48% by 2020 while the supply of oncologists will rise by 14% (3). As projected demand outpaces anticipated resources, the ASCO Workforce Advisory Group recommends improved integration of APPs into the oncology workforce (3).

The majority of APRNs are Nurse Practitioners (NPs) and the American Association of Nurse Practitioners (AANP) reports that there are over 205,000 NPs in the United States in 2015 with 1.2% of these NPs practicing in clinical oncology (4). Other APRNs in oncology include Certified Registered Nurse Anesthetists (CRNAs) and clinical nurse specialists (CNS). Meanwhile, the National Commission on Certification of Physician Assistants (NCCPA) reported 108,717 certified PAs in the United States in 2015 (5). Ross *et al.* (6) reported that approximately 2.4% of the 75,000 PAs in the United States in 2010 designated oncology as an area of clinical practice.

The APP scope of practice allows for significant contributions across the different stages of the cancer disease trajectory and APPs provide screening and prevention services, diagnosis and treatment, survivorship and surveillance, as well as end-of-life care (3,7-10). APPs can also be found in a variety of community, acute care, and tertiary practice settings in different oncology specialties. Research has documented that oncologists working in teams with APRNs and PAs report improved efficiency, patient

care satisfaction, and higher professional satisfaction (3). In the United States, there are states that allow NPs full practice authority without requirement of a signed practice agreement with a collaborating physician (11); however in the oncology specialty, APPs including NPs and PAs are part of an interdisciplinary team that develops plans for active cancer treatment with active engagement and direction of surgical oncologists, medical oncologists and radiation oncologists.

APP education and training vary according to professional track. In order to practice as an APP, one must successfully complete education, training, and then pass a national certification examination as a PA or APRN. Physician Assistant education and training is graduate level education in advanced anatomy, physiology, pharmacology, physical diagnosis, pathophysiology, microbiology, clinical and laboratory science, behavior science, and medical ethics (12) that culminates in entry level practice with a master's degree. Education and training includes rotations in family medicine, internal medicine, obstetrics and gynecology, pediatrics, general surgery, emergency medicine, and psychiatry (12). All PA students complete these core courses and training components along with electives in their area of interest. Most PA programs are three academic years in length and culminate in a master's degree (12). The education and training qualifies one for completion of a national certification examination necessary for entry level PA practice. There are also post graduate oncology fellowships for PAs in comprehensive cancer centers that allow for advanced specialization PA oncology practice. At MD Anderson Cancer Center, the one-year PA Fellowship program involves intensive training and instruction under senior oncology clinical PAs and PA educators in various hematology, oncology and solid tumor specialties.

For APRNs, the education and training is determined by the specialty that the APRN decides to pursue at the outset of his or her graduate level education. The most frequently encountered APRNs in oncology are NPs. NPs are Registered Nurses (RNs) who have completed additional graduate education and training to practice with an increased degree of autonomy in assessing health and medical problems as well as with prescribing and evaluating interventions. While the current entry level for NP practice is a Master of Science in Nursing (MSN) degree, the American Association of Colleges of Nursing (AACN) has recommended a shift in preparing NPs with a doctorate in order to enter practice with a Doctor of Nursing Practice or DNP degree (13). The length of a master's level NP program can range from 15–24 months (14) depending on the specialty focus and the NP student's part-time or full-time status. NP education comprises of advanced theoretical and clinical instruction on clinical subjects similar as those comprising the PA curriculum but NPs receive instruction emphasizing the development of clinical and professional expertise in a specialty area that the NP student decides to pursue at the outset of his or her program of study. The curriculum prepares the graduate to successfully complete the national certification in their chosen, anticipated area and population of specialty practice (13). The different NP specialty population foci include family health (individual across lifespan), neonatal, pediatrics, adult, gerontology, women's health, and mental health (14). Additional specialties such as oncology and acute care are also available for NPs (15).

The NP curriculum, regardless of population or specialty focus, incorporates training in competencies that develop scientific foundation, leadership, quality improvement competencies, practice inquiry skills, technology and information literacy, policy competencies, health delivery system competencies, ethics competencies, and independent practice competencies (16). These are designed to equip NPs with core competencies in health care quality improvement, informatics, and evidence-based practice so they can successfully function not only as advanced clinicians but also as valuable contributors and leaders of health care improvement initiatives.

Once in practice, APPs are licensed to diagnose and treat diseases as well manage symptoms. APPs are also licensed with prescriptive authority and can prescribe medications as part of their clinical duties. *Table 1* summarizes the services and responsibilities of APPs. Services provided by APPs in oncology were evaluated by the ASCO Study of Collaborative Practice Arrangements (SCPA) in a survey of 266 oncology practices, out of which 33 were selected based on practice size, structure, and geographic distribution (3). The results from the investigation of the study group revealed that APP services included performing clinical procedures, managing disease and treatment, and providing education and counseling. Duties such as chemotherapy orders, inpatient rounds, research-related activities, symptom management, survivorship care, end-of-life care, and providing non-cancer related primary care were also specified in the report. The various activities generally fall into clinical, education, research, and administrative categories. As the health

Table 1 APP services and responsibilities

Conduct medical history assessment and physical examination
Order, perform, and interpret diagnostic tests
Collaborate with physicians and other health professionals
Diagnose and treat acute and chronic conditions
Develop treatment plans
Prescribe medications and treatments
Assist in surgery
Counsel patients and family
Educate patients on disease prevention and health promotion

Source: AAPA (12), AANP (15). APP, Advanced Practice Provider; AAPA, American Academy of Physician Assistants; AANP, American Association of Nurse Practitioners.

care system continues to evolve, APPs are called upon in their various areas of oncology practice to optimize the integration of these responsibilities to help improve patient care outcomes.

Soreening & prevention programs

APPs provide many cancer screening and prevention services in collaboration with physicians, and the enactment of the Affordable Care Act is expected to increase the utilization of these services. A systematic review to evaluate the role of APPs in cancer screening and prevention examined 15 studies published from 1990–2011 (7). When evaluating breast cancer screening practices, studies reviewed showed that 69–91% of patients who saw APRNs received mammograms and that APRNs make mammogram recommendations similarly as physicians. An intervention study compared screening offered and conducted by an APRN during a routine clinic visit to a standard chart reminder system. This showed significantly higher increase in the annual rate of Pap smears and mammograms in the intervention group who received screening during their routine visit, compared to the increase in the annual rate of these screening activities through a chart reminder system (7,17). This supports the thoughtful and systematic use of APP resources in intervention programs that can help improve outcomes. Furthermore, APPs are also valuable resources in interdisciplinary practices for cancer prevention counseling. The systematic review showed that smoking cessation recommendations are provided routinely by both physicians and physician extenders; however, of the nine studies pertaining to tobacco cessation, three showed that patients are more likely to receive recommendations for smoking cessation during visits with APPs than during visits without them (7). With the demands and time constraints on physicians, it is essential to optimize APP utilization to improve screening and prevention programs.

In settings such as MD Anderson Cancer Center, APPs manage APP-staffed screening and prevention outpatient clinics. While physician collaboration and oversight is in place at these practices, APPs optimize their practice scope by providing services that include routine surveillance, screening services and procedures, review of diagnostic studies, education regarding screening practices. In some high-risk patient populations, APPs engage in discussion of chemoprevention options, including providing patients with risk profiles to better equip them to make well-informed decisions about preventative care. The benefits of APP utilization in this setting include improved access to evidence based care as well as cost-effective care. Understanding the scope of practice for APPs and allowing them to make the most of their education, training and skills is essential to optimizing the collaboration of health care givers within the interdisciplinary team.

Treatment and disease management settings

While APPs are of significant value to screening and prevention programs, their skills are most frequently utilized in the active treatment and management of cancer. APPs practice in the inpatient setting, outpatient clinics, and in the operating room. They practice in different clinical specialties within the surgical oncology, medical oncology, and radiation oncology disciplines alongside oncology physicians and other interdisciplinary experts. APPs are involved in reviewing referrals and directing patients to the appropriate clinics for their initial evaluation and diagnostic procedures. They collaborate with physicians to determine treatment decisions, oversee the coordination of care, conduct follow-up visits, and provide symptom management. In carrying out these functions, they are engaged as clinicians, educators, and patient advocates. They also collaborate during treatment and disease management by facilitating clinical trials and other research-related efforts. The 2011 ASCO Study of Collaborative Practice Arrangements noted that patients were satisfied when their care was provided by APPs, and that there was a reported increase in productivity in practices that utilized

APPs, and that physicians and APPs are highly satisfied with collaborative practices (3).

In the outpatient setting, APPs facilitate expeditious access for new patients who need evaluation for a newly diagnosed cancer or for a possible cancer diagnosis. There are APPs who work closely with the referral centers in large cancer centers to review cases with referring physicians and direct the patient to the appropriate medical or surgical clinics. APPs sometimes coordinate care with the referring physicians and the patients even before the patient's first visit. In surgical practices where surgeons have high-volume operative obligations precluding them from being able to conduct clinic consultations daily, their APP partners are available to evaluate patients and arrange appropriate diagnostic and staging tests that can expedite care. The surgeon and the interdisciplinary team can then evaluate and plan treatment with diagnostic information already available following a pre-consultation visit with the APP. In similar cases when surgeons are attending to operative cases, pre-operative and post-operative evaluations can be managed by the APPs. In the peri-operative setting, APPs provide surgical first-assist services by participating in operations ranging from relatively minor skin cancer excisions to major, multi-surgical service resections. In other medical specialties, APPs run fast-track clinics for patients who require lab monitoring and symptom management while on cancer treatment. In addition to managing APP-staffed clinics, they also see new and complex follow-up patients in collaboration with physicians. While APPs have the autonomy to carry out many services and collaborate with other health care providers to manage oncology patients in U.S., the plan for cancer resection, systemic cancer treatment, and radiation treatment requires the final authorization of the physicians whose active involvement and oversight is also required while the plan is implemented.

APPs dedicated to the inpatient setting provide the stability and expertise on the hospital units as they manage clinical concerns, patient education and counseling needs, and overall coordination of care. Many members of the interdisciplinary team including physicians often have outpatient clinic responsibilities or in the case of surgeons, operating room responsibilities so having inpatient APPs present on the hospital units provide the necessary first line presence in managing and coordinating the complicated care for hospitalized cancer patients. A recent retrospective study examined 95 patients with acute myelogenous leukemia (AML) admitted for re-induction chemotherapy from 2008–2012 into either a PA service or a resident service, both of which were overseen and supervised by faculty attending physicians (8). Forty-seven patients were admitted to the resident service while 48 were admitted to the PA service and results revealed equivalent mortality but with a statistically significant difference (P=0.03) in the shorter length of stay for the PA service (mean of 30.9 days) compared to the resident service (mean 36.8 days). The number of consults and the 14-day readmission rate also revealed a statistically significant difference in favor of the PA service (P=0.03). The 14-day readmission rate was 10.6% for the resident service while it was aero for the PA service. The mean number of consults also showed a statistically significant difference (P=0.03) and indicated a 2.11 consults (range, 0–5 consults) for the resident service and 1.47 (range, 0–4) for the PA service. Along with mortality, the ICU transfers did not reveal a significant difference between the two groups of caregivers working with faculty attending physicians (8). In services where physicians and medical trainees have obligations in different areas of the hospitals and clinics, there is support for advantages to having inpatient APPs focused on managing the hospitalized patients. More studies are needed to bear out these findings and examine other advantages of APP services in the acute inpatient management of different cancer patient populations.

The APPs' work from admission to discharge including post-discharge coordination with the patient's outpatient care givers is helpful with reducing readmissions, discharge delays, post-discharge clinic drop-in visits, and decreasing complication rates. At MD Anderson Cancer Center, inpatient APPs have also worked with physicians to develop and implement enhanced recovery programs and tele-medicine post-operative programs in an effort to improve surgical outcomes.

Survivorship care

With an increasing number of cancer survivors in the United States as well as a decrease in physicians entering the field of oncology, APPs have been identified as members of the healthcare team that can help balance the oncology supply and demand (McCabe & Pickard, 2012). APPs are trained such that they are well-equipped to provide the comprehensive care proposed for cancer survivors, including ongoing age-specific cancer screening, general wellness, disease prevention, counseling, and management of cancer therapy sequelae. Because of developments in early

detection and advances in treatment, the number of cancer survivors in the United States approaches 12 million with an estimated 7.2% of the general population aged 18 or older reporting a personal history of cancer (9). Additionally, many APPs manage APP-staffed clinics in the outpatient setting, which provide surveillance for recurrence, new cancer screening, identification and management of late effects of cancer treatment, and as previously discussed, health prevention measures.

The improvement in cancer therapies and the resulting reduction in mortality rates point to longer time periods that patients will live through the different phases of the disease; thus, contributing to an increased demand for symptom management and survivorship care (9). As such, APPs will be called upon to help reduce the gap in care, and to ensure that effective and efficient survivorship programs are in place to provide optimal patient management.

Palliative oare

Services that comprise palliative care include team-based care planning, pain and symptom management, communication with patients and families, ensuring continuity of care across range of clinical settings, attention of spiritual comfort and psychosocial support, bereavement support, and hospice care (Fox, 2014). APPs are not only well-positioned to provide these services but can also benefit the patient and the interdisciplinary team by leading special intervention programs that improve overall care and specific outcomes. A prospective randomized study examined the value of palliative interventions from an advanced registered nurse practitioner compared to standard care for patients with metastatic cancer (18). The investigators found that interventions from advanced practice nurse practitioners that included explanation of hospice benefits and discussion regarding advanced directives early in the course of treatment for metastatic disease lead to measurable, statistically significant improvements in the patients' reported emotional and mental quality of life (18). APPs can be utilized to lead intervention programs that provide added benefits to alleviate the distress of patients and families receiving end-of-life care.

Summary

The training and education of APPs afford them the special skill set to benefit patients and provide an essential resource to alleviating the burden associated with the projected shortage of oncology clinicians. APPs and physicians in collaborative oncology practices both report high satisfaction with the collaboration, and patients report that they are aware when being treated by an APP and indicate that they are very satisfied with the care they receive in these collaborative oncology practices (3). APPs can enhance the care oncology patients receive through interventions that improve the effective utilization of prevention and screening services as well as promoting high-quality care delivery and outcomes. Looking ahead to the future, APPs can continue their clinical contributions and education efforts to help prepare trainees for oncology care. Additionally, APPs can also enhance their research efforts and look into investigating innovative ways to improve care delivery and the quality of life for patients throughout the cancer illness experience. Information gleaned from these investigations can provide the foundation for advances in interdisciplinary cancer care and research.

Aoknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Reynolds RB, McCoy K. The role of Advanced Practice Providers in interdisciplinary oncology care in the United States. Chin Clin Oncol 2016;5(3):44. doi: 10.21037/cco.2016.05.01

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Journal Publications:

Reynolds, R.B., & McCoy, K. (2016). The role of Advanced Practice Providers in interdisciplinary oncology care in the United States. *Chinese Clinical Oncology*, 5(3):44. doi: 10.21037/cco.2016.05.01

Brana Reynolds, R., & Folloder, J.P. (2014). Clinical management of pancreatic cancer. *Journal of the Advanced Practitioner in Oncology,* 5(5)356-364.

Brana Reynolds, R., & Folloder, J.P. (2014). Use of radiographic criteria to predict outcomes after surgery for pancreatic cancer. *Journal of the Advanced Practitioner in Oncology,* 5(5), 365-370.

Book Chapter:
Braña, R.H., & Evans, D.B. (2003). Thyroid and adrenal cancer. In *Cambridge Handbook for Advanced Cancer Care,* ed. M.J. Fisch, E. Bruera. pp 294-299. Cambridge University Press; NY.

AWARDS AND RECOGNITION

American Cancer Society Doctoral Scholarship in Cancer Nursing	2017-2018
Surgical Oncology Performance Reward	2017
Oncology Nursing Society Foundation Research Doctoral Scholarship	2016
American Cancer Society Doctoral Scholarship in Cancer Nursing	2015-2017
MD Anderson Nursing Excellence Award – Dawn Gross Memorial Scholarship	2015
Oncology Nursing Society Foundation Connections Grant	2013
Department of Surgical Oncology Cut-Above Award	2005, 2006, 2008
Sigma Theta Tau International Honor Society for Nursing	1992
National Dean's List Award of Merit	1992
Philippine Nurses Association Student Scholarship Award	1990

ABSTRACTS ACCEPTED FOR PRESENTATION:

1. **Reynolds, Rae Brana**. *Adrenal Incidentalomas.* Accepted for National Nurse Practitioner Symposium. Keystone, CO. (Upcoming symposium July 2018)

2. **Reynolds, Rae Brana**. *Pancreatic Cancer: Update on Evaluation and Treatment.* Accepted for National Nurse Practitioner Symposium. Keystone, CO. (July 2017)

3. Schacht, Elizabeth & **Reynolds, Rae Brana**: *Parathyroid Carcinoma Overview: A Case Study*. Accepted for JADPRO (Journal of the Advanced Practitioner in Oncology) Live at APSHO (Advanced Practitioner Society for Hematology and Oncology) Conference. National Harbor, MD. November 2016.

4. Maria Q Petzel, Sarah Thornton, Vanessa Martinez, Hsiang Chun Chen, Xuemei Wang, Jason B Fleming, Jeffrey E Lee, Justin Folloder, Carol Clegg, **Rae Reynolds**, Matthew H Katz. *Nutrition status correlates with patient-reported quality of life prior to treatment for pancreatic adenocarcinoma.* Accepted for poster presentation. Pancreas Club Annual Meeting. San Diego, CA. May 2016.

5. **Reynolds, Rae Brana**. *Thyroid Nodules: When to perform FNA and what do FNA results mean?* Accepted for the American Association of Nurse Practitioners National Conference. Las Vegas, NV. June 2013

6. **Reynolds, Rae Brana**. *Adrenal Incidentalomas: Update on Evaluation and Management*. Accepted for the American Academy of Nurse Practitioners 27th National Conference. Orlando, FL. June 2012

7. **Reynolds, Rae Brana**. *Pancreas Cancer: Is it Resectable?* Accepted for the American Academy of Nurse Practitioners 26th National Conference. , Las Vegas NV. June 2011

8. **Brana, Rae Zyn**. *Hyperparathyroidism*. Accepted for the American Academy of Nurse Practitioners 25th National Conference. Phoenix, AZ. June 2010

9. **Brana, Rae Zyn**. *Multiple Endocrine Neoplasia Type 1*. Accepted for the American Academy of Nurse Practitioners 24th National Conference. Nashville, TN. June 2009

10. **Brana, Rae Zyn**. *Surgical Treatment for Pancreas Cancer*. Accepted for the American Academy of Nurse Practitioners 23rd National Conference. Washington DC. June 2008

11. Brana, Rae Zyn. *Thyroid Cancer: Update on Evaluation and Treatment*. Accepted for the American Academy of Nurse Practitioners 22nd National Conference. Indianapolis, IN. June 2007.

12. **Brana, Rae Zyn.** *Pancreas Cancer: Update on Evaluation and Treatment*. Accepted for the American Academy of Nurse Practitioners 21st National Conference. Grapvine, TX. June 2006

13. **Brana, Rae Zyn.** *Evaluation of Adrenal Lesions*. Accepted for the American Academy of Nurse Practitioners 20th National Conference. Fort Lauderdale, FL. June 2006

14. **Brana, Rae Zyn**. *Hyperparathyroidism: Evaluation and Management*. Accepted for the American Academy of Nurse Practitioners 19th National Conference. New Orleans, LA. June 2005

PROFESSIONAL PRESENTATIONS:

1. *The Role of Advanced Practitioners in Optimizing Care for HPB Patients: USA Experience*
   Invited speaker at International Hepato-Pancreato-Biliary Association World Congress
   Congress scheduled for September 4 – 7, 2018; Geneva, Switzerland

2. *Adrenal Incidentalomas*
   National Nurse Practitioner Symposium. (Abstract accepted for July 19, 2018)
   Keystone, CO

3. *Primary Adrenal Malignancies*
   Asssociation of Physician Assistants in Oncology Conference (August 25, 2017)
   San Diego, CA

4. *Pancreatic Cancer: Update on Evaluation and Treatment*
   National Nurse Practitioners Symposium (July 20, 2017) Keystone, CO

5. *Career Trajectories in Nursing*
   Central Philippine University, College of Nursing (June 17, 2015) Iloilo City, Philippines

6. *Nursing Career Trajectorie*s
   Philippine Nurses Association Meeting (June 18, 2015) Iloilo City, Philippines

7. *Glioblastoma Multiforme Survival Analysis*
   University of Texas – Houston Research Day (April 2014) Houston, TX

8. *Surgical Management of Pancreas Cancer*
   Houston Area Nurse Practitioners Annual Conference (August 2013) Houston, TX

9. *Thyroid Nodule FNA – What does the pathology report mean?*
   AANP 28th National Conference for Nurse Practitioners (June 2013) Las Vegas, NV

10. *Adrenal Incidentalomas*
    AANP 27th National Conference for Nurse Practitioners (June 2012) Orlando, FL

11. *The Role of the Mid-Level Provider in Long Term Surveillance Programs*

Americas Hepato-Pancreato-Biliary Association Annual Meeting (March 2012) Miami, FL

12. *Pancreas Cancer: Is it Resectable?*
AANP 26th National Conference for Nurse Practitioners (June 2011) Las Vegas, NV

13. *Hyperparathyroidism*
AANP 25th National Conference for Nurse Practitioners (June 2010) Phoenix, AZ

14. *Multiple Endocrine Neoplasia*
AANP 24th National Conference for Nurse Practitioners (June 2009) Nashville, TN

15. *Pancreas Cancer Update*
3rd Annual Current Trends in Oncology Nursing (January 2009) Park City, UT

16. *Schwartz Rounds Presenter*
Oncology Congress 2008 (October 2008) San Francisco, CA

17. *Surgical Treatment for Pancreas Cancer*
AANP 23rd National Conference for Nurse Practitioners (June 2008) Washington DC

18. *Hypercalcemia in Malignancy*
Annual Infusion Nursing Society Meeting (May 2008) Phoenix, AZ

19. *Current Trends in Oncology Nursing – Session Moderator*
Current Trends in Oncology Nursing (January 2008) Park City, UT

20. *Thyroid Cancer: Update on Evaluation and Treatment*
AANP 22nd National Conference for Nurse Practitioners (June 2007) Indianapolis, IN

21. *Integrating Opioids and Invasive Procedures in Cancer Pain Management*
Current Trends in Oncology Nursing (January 2007) Steamboat Springs, CO

22. *Pancreas Cancer: Update on Evaluation and Treatment*
AANP 21st National Conference for Nurse Practitioners (June 2006) Grapevine, TX

23. *Pancreas Cancer: Update on Evaluation and Treatment*
Oncology Nursing Society Congress (May 2006) Boston, MA

24. *Evaluation of Adrenal Lesions*
AANP 20th National Conference for Nurse Practitioners (July 2005) Fort Lauderdale, FL

25. *Thyroid Nodules and Thyroid Cancer: An Update*
Texas Women's University Student In-Service (October 2004) Houston, TX

26. *Thyroid Nodules and Thyroid Cancer: An Update*
Philippine Nurses Association Seminar (September 2004) Houston, TX

27. *Hypercalcemia and Hyperparathyroidism*
AANP 19th National Conference for Nurse Practitioners (July 2004) New Orleans, LA

28. *Surgical Treatment of Pancreas Cancer*
Gastrointestinal Center (July 2003) M.D. Anderson Cancer Center, Houston, TX

29. *Nursing Care for the Patient Undergoing a Pancreaticoduodenectomy*
Gastrointestinal Center (November 2001) M.D. Anderson Cancer Center, Houston, TX

30. *Methadone for Cancer Pain*
Symptom Control and Palliative Care Grand Rounds (March 2001)
M.D. Anderson Cancer Center, Houston, TX

31. *Use of Methadone in Cancer Pain*
Oncology Update: Advances and Controversies (Feb 2001) Steamboat Springs, CO

PROFESSIONAL MEMBERSHIPS:

Texas Nurse Practitioners	2012 - present
Oncology Nursing Society	2000 – present
Sigma Theta Tau, International Honor Society for Nursing	1992 – present
American Association of Nurse Practitioners	2006 - present

COMMUNITY SERVICE

Marit Peterson Foundation Melanoma Research Fund Annual Event
Surgical Oncology Advanced Practice Providers Community Outreach Programs
Annual Melanoma AIM Walk, MD Anderson Cancer Center