Alternate Genetic Services Delivery Models for Individuals with Pancreatic Cancer: An Investigation of Patient Reported Knowledge and Distress Levels

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Christine Marie Drogan

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This thesis was presented

by

Christine Marie Drogan

It was defended on

April 14, 2020

and approved by

Randall Brand, MD, Professor of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, School of Medicine, University of Pittsburgh

Robin E. Grubs, MS PhD LCGC, Associate Professor of Human Genetics, Director, Genetic Counseling Program, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Phuong Mai, MD MS, Associate Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine, University of Pittsburgh

John Shaffer, PhD, Assistant Professor, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Thesis Advisor: Beth Dudley, MS MPH LCGC, Adjunct Instructor, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh
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Christine Marie Drogan, MS
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Abstract

An estimated 57,600 people in the United States will be diagnosed with pancreatic ductal adenocarcinoma (PDAC) in 2020. Efforts in the age of precision medicine focus on early detection and tailored treatments, of which germline genetic testing is a vital component. An estimated 10% of individuals with PDAC have a germline pathogenic variant. Increased risk of PDAC can be observed in multiple hereditary predisposition cancer syndromes, which have implications for a patient and their family members. Affected mutation carriers may have longer survival when treated with platinum-based therapies, PARP inhibitors, and anti-PD1 therapy. Unaffected mutation carriers may benefit from high-risk imaging surveillance protocols. These medical management implications make genetic testing for individuals with PDAC and their family members an important public health initiative. As such, national professional groups have recommended all PDAC patients have a genetics evaluation ideally conducted by a genetics professional; however, due to the genetic counselors shortage, exploration of alternative methods of service delivery is necessary to increase accessibility. In January 2020, the University of Pittsburgh Medical Center (UPMC) implemented a 5-minute educational video tailored to individuals with PDAC to increase germline testing access. This pilot study aimed to evaluate the effect of two delivery modes on participant knowledge and distress levels: an abbreviated genetic counseling session with a licensed and certified genetic counselor, or the educational video.
Genetic literacy was evaluated prior to genetics education. Knowledge was measured immediately following education. For individuals who underwent genetic testing, knowledge assessment was repeated 2 weeks after results disclosure; a questionnaire (MICRA) that assesses the impact of genetic testing results on distress was also administered at the post-disclosure timepoint. Due to the small sample size, nonparametric tests were used (n=14). Knowledge and distress levels were compared between educational groups and were found to be not significantly different, indicating that video education provides timely genetic testing access to patients with PDAC without compromising educational value or causing undue distress. Understanding knowledge acquisition and distress among participants undergoing video genetic education may inform future alternative service delivery models, which in turn affects public health initiatives in genetic services.
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Preface

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And to her family, classmates, and professors in the Department of Human Genetics.
1.0 Introduction

The goal of this pilot study was to evaluate the use of video education for individuals with pancreatic ductal adenocarcinoma (PDAC) by measuring knowledge at two time points, as well as post-testing psychological distress. Up to 10% of individuals with PDAC have a clinically actionable germline pathogenic variant identified through multi-gene panel testing, which affects not only what treatments they may be eligible for, but also has implications for family members.\textsuperscript{1,2,3} At the University of Pittsburgh Medical Center (UPMC), patients with PDAC are often referred to genetic counselors in the Hereditary GI Tumor Clinic, however many do not follow through with their appointment. Additionally, wait times for genetic counseling appointments can be long, and it is possible that someone with PDAC can die before their evaluation.

When two national organizations, the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN), changed their guidelines to recommend all individuals with PDAC have a genetics evaluation, the Hereditary GI Tumor Clinic strategized methods to implement a universal testing protocol so that all individuals with PDAC at UPMC would have access to genetic services.\textsuperscript{4,5} UPMC has a designated multidisciplinary clinic (MDC) for patients with newly diagnosed PDAC in which providers from different specialties meet with patients and families in one setting. Because this structure was already present at UPMC, having genetic services available at this initial visit was the most efficient way to accomplish the goal of developing a universal genetic testing approach that was feasible for broader implementation among the large UPMC network of cancer centers and hospitals. This initiative began in January 2020.
The MDC for PDAC is held at two different UPMC sites, Hillman Cancer Center and Presbyterian Hospital. Even though there are two genetic counselors who specialize in gastrointestinal cancer genetics at UPMC, their workload does not allow them to see all patients newly diagnosed with PDAC through the MDC. Furthermore, the shortage of genetic counselors in the UPMC network system, analogous to the shortage in the United States, highlights the need to explore alternate forms of service delivery to provide services for more patients who require genetic counseling services. In order to deliver genetic information to patients seen at the MDC, a 5-minute video specifically related to the genetics of pancreatic cancer was developed to discuss the implications of genetic testing for this specific patient population.

This study was developed to assess the use of video education, and to determine whether it was a practical and effective way to increase access to genetic information in a population who were candidates for genetic testing.

This pilot study had two specific aims:

(a) To compare pancreatic cancer genetic knowledge between a group who received traditional genetic counseling and a group who watched an educational video.

(b) To compare distress, uncertainty, and positive experiences after genetic testing results disclosure between the two groups.

A randomized model was implemented in order to measure participants’ knowledge over time and emotional distress following results disclosure, with the aims of comparing them between the two groups to assess the utility and efficacy of video education. The results of this study may help determine whether patients with PDAC seen throughout the UPMC network including the UPMC PDAC MDC can receive genetic education by video without adverse
outcomes and allow genetic counselors to focus their appointments for those patients who have a positive genetic test result or require a more detailed conversation.
2.0 Literature Review

2.1 Pancreatic Cancer

Annually, the American Cancer Society (ACS) publishes estimates of new cancer diagnoses and deaths based on recent data. The ACS estimates that 57,600 people in the United States will be diagnosed with pancreatic cancer in 2020, with an average age of diagnosis of 71. The ACS also estimate 45,050 deaths as a result of this disease in 2020. Pancreatic cancer affects slightly more men (52.8%) than women (47.2%), however it is the 4th most common cancer death among both sexes. The incidence rate of pancreatic cancer continues to rise; however the 5-year survival rate remains at 9%. The stage of disease at diagnosis affects overall prognosis, however even the rare subset of patients with a localized cancer at diagnosis (10% of diagnoses) only have a 5-year survival rate of 34%.

Patients with pancreatic cancer rarely show symptoms until the disease has advanced, and because of this, it is one of the hardest cancer types to treat. The presenting symptoms of pancreatic cancer are relatively non-specific and can include weight loss, jaundice, and abdominal or back pain. At the time of symptom presentation, 60% of pancreatic cancers will be metastatic. Studies of abdominal imaging have found changes suspicious for pancreatic cancer one year before diagnosis, which indicates that perhaps there is a timeframe for earlier detection of cancer.

Another reason pancreatic cancer is often not identified before it becomes locally advanced or even metastatic is due to poor screening options. Biomarkers like CA19-9 are elevated in 87% of individuals with pancreatic cancer, but measuring CA19-9 levels has not proven
to have utility when screening asymptomatic individuals. Imaging studies like abdominal CT or MRI are available, however they cannot detect tumors smaller than 2cm in size, and therefore, may not be useful as a screening tool in asymptomatic patients.

2.2 Risk Factors for Pancreatic Cancer

There are several risk factors for pancreatic cancer, some of which are modifiable, like tobacco use and body mass index (BMI), while others are not, like age and family history. The modifiable risk factor most strongly associated with an increased risk is smoking, conferring a 74% increased risk for current smokers, and 20% for former smokers. The risk associated with smoking persists for 10-20 years following smoking cessation. Studies of alcohol consumption and pancreatic cancer have shown variable association. Alcohol abuse is a risk factor for chronic pancreatitis, which is known to increase risk of pancreatic cancer. Additionally, studies have shown that cigarette smoking and alcohol consumption are linked to diagnoses of pancreatic cancer at younger ages. Type 2 diabetes is associated with an increased risk of pancreatic cancer. Even obesity in the absence diabetes increases the risk of pancreatic cancer, and is estimated every additional 5 BMI units increases the risk of pancreatic cancer by 10%. One type of infection, Helicobacter pylori, is associated with a 45% increase in risk, and can be treated with antibiotics when detected.

In addition to modifiable risk factors of pancreatic cancer, there are also unmodifiable factors that increase the risk for pancreatic cancer. The risk of pancreatic cancer increases with age; 90% of pancreatic diagnoses occur after age 55, with only rare cases occurring before age 30. Most diagnoses occur during the 7th and 8th decade of life. Pancreatic cancer occurs slightly more
frequently in males, however the discrepancy between sexes is more exaggerated in developed countries. Researchers have hypothesized that estrogen exposure may account for some of the observed sex differences. However, studies have not identified an association between estrogen exposure and risk of pancreatic cancer, indicating that males may be exposed to more environmental risk factors or genetic factors. Additionally, the incidence of pancreatic cancer differs among races, with the highest rates in the African American population, and the lowest rates in Pacific Islanders and Asian-Americans. This could be due to the higher incidence of diabetes and smoking in the African American population, although there is evidence that genetic factors also may play a role in this difference. Blood group and the microbiome could also influence one’s likelihood to develop pancreatic cancer. Pancreatic cystic neoplasms like intraductal papillary mucinous neoplasms (IPMN), are common in the general population, and proper management of them could prevent progression of a benign cyst to pancreatic cancer. After five years, 6.9% of IPMNs progressed to pancreatic cancer. Lastly, there is strong evidence that family history of pancreatic cancer and genetic susceptibility influences the chance that a person develops pancreatic cancer during their life. The risk is estimated to be 6.4-fold if an individual has two affected first degree relatives (FDR) (conferring a 8-12% lifetime risk) and 32-fold in individuals with three or more affected FDRs (amounting to a 40% lifetime risk). Those with a hereditary predisposition to cancer may have a lifetime risk greater than 5%, depending on the gene that harbors the pathogenic variant. However, it is estimated that only 20% of familial clusters of pancreatic cancer have an identifiable germline pathogenic variant.
2.3 Pancreatic Cancer and Genetics

Generally, germline genetic testing is able to identify individuals who may benefit from increased surveillance and other prevention efforts, particularly breast, ovarian and colon cancer.\(^1\) Traditionally, individuals with pancreatic cancer have not benefitted from these options given the poor survival rates. Recently, though, it has been recognized that there is clinical utility to identifying pathogenic variants in individuals with pancreatic cancer, as there is potential for implementing a precision medicine approach for treatment.\(^{21}\) An estimated 5-10% of individuals with pancreatic cancer have an identifiable germline pathogenic variant.\(^{1,2}\) There are multiple cancer predisposition syndromes that are associated with an increased risk of pancreatic cancer, including Hereditary Breast and Ovarian Cancer syndrome, Lynch syndrome, Peutz-Jeghers syndrome, Familial Atypical Multiple Mole Melanoma, Familial Adenomatous Polyposis, and Li Fraumeni syndrome.\(^{22}\) However, pancreatic cancer is not the predominant cancer type observed in these inherited predisposition syndromes.\(^{23}\)

One study of germline testing in affected individuals found that having a mutation was significantly associated with having a first degree relative with breast or colon cancer, but not a family history of pancreatic cancer. Some evidence suggests that individuals with a family history of pancreatic cancer may be diagnosed at younger ages than those without a family history, but a number of studies have found that age of diagnosis is a poor predictor for presence of a germline pathogenic variant.\(^{2,8}\) Germline mutation status was also not associated with stage of pancreatic cancer diagnosis.\(^{24}\) Another study performed genetic testing on 176 patients with pancreatic cancer, regardless of whether or not they met current germline genetic testing guidelines. Forty-four individuals (25.0%) were found to have a pathogenic variant, 17 of which were in \(BRCA1\) or \(BRCA2\).\(^{25}\) Because this study included those who did not meet testing criteria, it is probable that
some of these mutation carriers could have been missed by the testing guidelines in 2017. This finding was replicated in another study, which showed that 26% of affected individuals with germline mutations did not meet testing criteria. Because of findings like these, in 2018 the American Society of Clinical Oncology (ASCO) established an expert panel which published a provisional clinical opinion (PCO) stating that all individuals with pancreatic adenocarcinoma, regardless of family history, should undergo risk assessment for inherited predisposition syndromes associated with increased risk of pancreatic cancer. Shortly after ASCO published their new guidelines, the National Comprehensive Cancer Network (NCCN) published new practice guidelines, which included germline genetic testing for all patients with pancreatic adenocarcinoma. Individuals should be tested with a panel test that analyzes all genes related to hereditary cancer syndromes that result in an increased risk for pancreatic cancer.

Hereditary Breast and Ovarian Cancer syndrome (HBOC), is a well-defined autosomal dominantly inherited predisposition syndrome caused by pathogenic variants in BRCA1 and BRCA2. HBOC is characterized by substantially increased risks of breast and ovarian cancer, however other malignancies are observed as well, such as pancreatic cancer, male breast cancer, prostate cancer, and melanoma. Studies investigating pancreatic cancer risks in BRCA1/2 mutation carriers have identified relative risk estimates ranging from 2.3-7. One study of individuals with newly diagnosed pancreatic ductal adenocarcinoma identified a BRCA1/2 pathogenic mutation in 4.6% of patients. The study identified three BRCA1 mutations and 11 BRCA2 mutations. The researchers also noted that the majority of mutation carriers did not meet genetic testing criteria. Another study of 151 high-risk pancreatic cancer families identified five pathogenic BRCA2 variants. Four out of five mutation carriers were diagnosed under age 55, which accounted for 10% of all individuals with an early onset diagnosis. Interestingly, the researchers did not identify
BRCA2 pathogenic variants in families with three or more affected FDRs, indicating that perhaps moderate-risk pancreatic cancer families, but not high-risk families are more likely to have a BRCA2 pathogenic variant.24 Pathogenic germline variants in PALB2, also called partner and localizer of BRCA2, result in an increased risk of mainly breast cancer, and to a lesser degree, pancreatic cancer. One whole exome sequencing study of 96 individuals with familial pancreatic cancer identified three truncating PALB2 mutations.28 Approximately 6% of pancreatic ductal adenocarcinoma diagnoses are caused by pathogenic variants in BRCA1, BRCA2 and PALB2.29

Germline pathogenic variants in ATM are associated with a moderately increased risk of breast cancer, as well as increased risk of pancreatic, prostate and possibly other cancer types. Cancer susceptibility associated with pathogenic variants in ATM is inherited in an autosomal dominant fashion; biallelic pathogenic variants in this gene cause ataxia telangiectasia. One study performed germline testing on 3030 patients diagnosed with pancreatic cancer and found 69 out of 253 (27.3%) germline pathogenic variant carriers had an ATM mutation. The mutation rate in controls was 0.37%, while in cases was 2.30% (p-value <0.001).1 In families with three or more affected people, 4.6% were found to have a pathogenic ATM mutation.30

Lynch syndrome is an autosomal dominant cancer predisposition syndrome caused by pathogenic variants in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2, as well as EPCAM. Individuals with Lynch syndrome are at an increased risk for colorectal and endometrial cancer, but ovarian, brain, gastric, small bowel, hepatobiliary tract, renal pelvis, ureter, and pancreatic cancers are also observed in higher frequencies than the general population.31,32 One study of 31 families with Lynch syndrome identified 47 cases of pancreatic cancer, with 13 families with two or more family members with pancreatic adenocarcinoma.32 In comparison to the general population, individuals with Lynch syndrome have a 8.6-fold increase
risk of pancreatic cancer, which is equal to a 3.7% lifetime risk.\textsuperscript{32,33} When pancreatic cancer occurs in patients with Lynch syndrome, it is often described to have a medullary appearance, with invasion into the lymph nodes and has microsatellite instability.\textsuperscript{33} Individuals with germline mutations in \textit{MLH1} or \textit{MSH2} have a higher risk of pancreatic cancer than those with \textit{MSH6} or \textit{PMS2} mutations.\textsuperscript{32}

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited predisposition syndrome caused by pathogenic variants in \textit{STK11}. It is characterized by hamartomatous polyps throughout the gastrointestinal tract and mucocutaneous hyperpigmentation. A meta-analysis found that individuals with PJS have a 132-fold higher risk of pancreatic cancer. This study also showed the cumulative risk of pancreatic cancer in individuals ages 15-64 with PJS is 36\%.\textsuperscript{34} Another meta-analysis found that the prevalence of PJS patients with pancreatic lesions that were successfully identified via surveillance was 12.2\%, the highest among all inherited predisposition syndromes and individuals with familial pancreatic cancer.\textsuperscript{35}

Familial Atypical Multiple Mole Melanoma (FAMMM) is an autosomal dominant inherited predisposition to cancer caused by pathogenic variants in \textit{CDKN2A}. This syndrome is characterized by increased risk for cutaneous malignant melanoma and pancreatic cancer. Among individuals with pancreatic cancer and a family history of melanoma, 7.8\% will have a pathogenic mutation in \textit{CDKN2A}. However, individuals without family history of melanoma have been reported to have \textit{CDKN2A} mutations as well, illustrating the variable expressivity of the condition.\textsuperscript{23} In a study of 1537 individuals with pancreatic cancer, nine (0.6\%) were found to have a pathogenic mutation in \textit{CDKN2A}. Twenty-six individuals had a personal history of both pancreatic cancer and melanoma, and 7.7\% of these were found to have FAMMM. Additionally, 3.3\% of people with a personal history of pancreatic cancer and a first degree relative with
pancreatic cancer were found to have a CDKN2A pathogenic variant.\textsuperscript{36} When comparing pancreatic cancer predisposition genes to one another, those with a CDKN2A pathogenic variant were the only people likely to have a family history of pancreatic cancer.\textsuperscript{1} Individuals with a CDKN2A pathogenic variant have an increased risk of pancreatic cancer by a factor of 13.1.\textsuperscript{37} The risk for an individual with FAMMM to develop pancreatic cancer by age 75 is about 17%. Interestingly, the researchers found that in their cohort of 19 FAMMM families, only seven (36.8\%) had a history of pancreatic cancer.\textsuperscript{38} The risk of pancreatic cancer is also increased (relative risk of 4.9) for non-mutation carriers in FAMMM families.\textsuperscript{36} There are no genotype-phenotype correlations in CDKN2A for pancreatic cancer risk.\textsuperscript{37}

Familial Adenomatous Polyposis (FAP), an autosomal dominantly inherited cancer predisposition syndrome, is caused by pathogenic variants in APC. It is characterized by numerous tubular adenomas throughout the colon and upper gastrointestinal tract, resulting in a nearly 100\% risk of colon cancer by age 40 if the colon is not resected.\textsuperscript{39} Extraintestinal cancers, while less commonly seen than intestinal cancers in individuals with FAP, have been observed, namely thyroid and pancreatic cancer.\textsuperscript{40} In polyposis patients and at-risk family members, the risk of pancreatic cancer is 4.46 higher than that of the general population. After individuals with FAP have a colectomy, their highest risk of cancer is ampullary (5-6\%), which could be confused with pancreatic cancer when reporting family history.\textsuperscript{41} Atypical pancreatic neoplasms seem to be reported more frequently in the literature, although this is perhaps due to a reporting bias.\textsuperscript{42}

Li-Fraumeni syndrome (LFS) is an autosomal dominantly inherited cancer predisposition syndrome caused by pathogenic variants in TP53. TP53 is a tumor suppressor gene and plays a major role in cell cycle regulation. Because of this, individuals with LFS have an increased risk of many cancer types, namely breast, sarcoma, leukemia, brain, and adrenal cancer, however other
cancer types can be seen. In an examination of 28 families with LFS, having a TP53 pathogenic variant was moderately associated with an increased risk of pancreatic cancer (p-value <0.02). Pancreatic cancer was the only adult onset cancer type besides breast cancer to be associated with LFS. Another study found that pancreatic cancer was significantly more frequent in individuals with LFS as compared to the general population, with a relative risk of 18.

Chronic Pancreatitis (CP) is a complex and progressive disease that involves chronic inflammation of the pancreas, leading to atrophy, fibrosis, dysplasia, deficiency of endocrine or exocrine function, abdominal pain and more. The International Pancreatitis Study Group found that the risk of pancreatic cancer in individuals with CP is 1.8% after 10 years, and increases to 4% after 20 years. Although 42-77% of CP cases are caused by alcohol abuse and other environmental factors like smoking, there are four genes that have been linked to CP. One study showed that 64 out of 134 patients with idiopathic CP (47.8%) were found to have a mutation in PRSS1, CFTR, CRTC, or SPINK1. Hereditary chronic pancreatitis is an autosomal dominant disease with 80% penetrance. In general, individuals are described as having hereditary CP when they have no other detectable cause of pancreatitis and have at least one first or second degree relative with pancreatitis. In one study, 52% of individuals with hereditary pancreatitis were found to have a pathogenic variant in PRSS1. Of those with a PRSS1 mutation, 11% did not meet clinical diagnostic criteria for hereditary pancreatitis. On observation of the 150 kindreds who had genetic testing, 84 (56%) appeared to have autosomal dominant CP. Only 1% of CP cases are caused by mutations in PRSS1.

Familial Pancreatic Cancer (FPC) is characterized by a family with at least two first degree affected relatives in which no genetic mutation has been identified. No obvious differences between sporadic pancreatic cancer (SPC) and FPC in regards to molecular biology and pathology.
of the cancer have been observed, although in FPC, multiple precancerous lesions like intraductal papillary mucinous neoplasms have been seen more frequently than in SPC. Unlike other tumor types, only 20% of FPC cases are found to have a germline pathogenic variant. There are potentially other genes that cause an increased risk of pancreatic cancer that have not yet been discovered. Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) and novel genes that increase the risk of pancreatic cancer, which could possibly account for the phenotype of some FPC cases.

2.4 Surveillance for Unaffected At-Risk Individuals

The incidence of pancreatic cancer in the general population is about 1.3% over a person’s lifetime, therefore screening is not recommended for the general population. It is generally accepted that individuals who have an increased risk of pancreatic cancer due to a germline pathogenic variant and/or family history may consider surveillance. Surveillance for pancreatic cancer offers the only early detection opportunity for pancreatic cancer, however there may be limited clinical utility unless indicated by personal or family history for individuals under age 50.

In 2019, the International Cancer of the Pancreas Screening (CAPS) Consortium revised their consensus statement regarding pancreatic cancer screening for individuals with an increased risk. Three categories of patients meet criteria for pancreatic cancer surveillance. The first group of individuals that are considered high-risk are those with a \textit{STK11} or \textit{CDKN2A} pathogenic variant, regardless of family history of pancreatic cancer due to their high lifetime risk of pancreatic cancer. The next group of individuals who qualify for surveillance are those with a pathogenic variant in \textit{BRCA1/2}, \textit{ATM}, \textit{PALB2} or \textit{MSH1/MSH2/MSH6} who have at least one first degree relative with
pancreatic cancer. Lastly, individuals with no identified pathogenic variant may be eligible for pancreatic cancer surveillance if they meet criteria for familial pancreatic cancer (FPC), which is defined as an individual with at least two affected family members who are first degree relatives of each other, of whom at least one is a first degree relative of the individual being considered for surveillance. There are no recommended surveillance procedures for individuals with FAP due to the low penetrance of pancreatic cancer, limited research on pancreatic cancer in FAP families and the general difficulty of pancreatic surveillance.

The new guidelines recommend that those being surveilled for a family history alone should begin surveillance by endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MCRP) at age 50 or 55, or 10 years before the earliest diagnosis in the family. For those with a pathogenic variant in BRCA1/2, ATM, PALB2, or MLH1/MSH2, surveillance is recommended to start at age 45 or 50, or 10 years before the earliest diagnosis in the family. Individuals with a pathogenic variant in STK11 or CDKN2A, MRCP and/or EUS are recommended every year beginning at age 40. Surveillance should be continued annually regardless of an unremarkable scan. Individuals with hereditary pancreatitis, regardless of gene status, are recommended to begin surveillance at age 40, or 20 years after their first pancreatitis attack. The CAPS Consortium notes that their recommendation of screening is based more on the increased risk, rather than efficacy of screening techniques. Regardless, surveillance for high-risk individuals should be performed by a team with expertise on detection and management.

MRCP and EUS are two imaging tests that are often used for surveillance and early detection for individuals at increased risk of pancreatic cancer. A study compared these two imaging tools for 139 high risk individuals undergoing baseline surveillance and found moderate
concordance in the detection of pancreatic lesions, as well as their size and location. The results found that EUS is better at detecting solid pancreatic masses, while MRCP is more accurate at detecting cysts, indicating that the imaging modalities are complementary, and one does not replace the other. The study also found that there was higher concordance between the imaging techniques at the participant’s 12-month follow up, although this could be because at this time those reading the images were aware of the baseline imaging results. CT scans have also been used by some centers as part of the International Cancer of the Pancreas Screening (CAPS) Consortium for early detection, however when compared to MRCP and EUS the overall detection rate was lower. CAPS recommends alternating of MCRP and EUS, however the consortium has not reached agreement on if or how to alternate these modalities. In addition, obtaining a fasting blood glucose level or HbA1c routinely at the time of surveillance is recommended.

A cost analysis of screening high risk individuals with FPC, PJS, hereditary pancreatitis, or FAMMM was performed and different imaging studies were compared to one another. Abdominal MRI/MRCP was found to have the highest average cost to Medicare at $659.37, and EUS had the highest out of pocket costs for patients. The study also estimated the cost of MRI/MRCP over a 20-year period for high risk populations to be $26,374.80. Screening for those with newly diagnosed diabetes over age 50 and associated weight loss or a personal history of smoking was the least expensive. Based on efficacy of detecting small lesions and moderate cost, the researchers concluded that MRI/MRCP is the best tool for surveillance of high risk individuals. The researchers argue that lower out of pocket costs for patients may increase compliance with screening recommendations and therefore cause earlier detection of pancreatic cancer. A cohort of patients undergoing surveillance for familial pancreatic cancer (FPC) and hereditary pancreatitis (HP) found that surveillance of those with FPC is more cost effective than those with HP.
2.5 Implications for Affected Individuals

Timely genetic germline testing for patients with pancreatic adenocarcinoma is important not only to inform risk for family members, but also for treatment decision making purposes. There are specific chemotherapy options available to those with pancreatic cancer who harbor a germline pathogenic variant or specific tumor characteristics.

Individuals with pathogenic variants in BRCA1/2 with extra-pancreatic cancers have more sensitivity to platinum-based chemotherapy, which target cancer cells with a high mutation burden. BRCA1/2 are involved in DNA repair, and when a germline pathogenic variant is present, the amount of mutations in tumor cells increase, which increases sensitivity to platinum therapies. A retrospective study patients with pancreatic cancer compared BRCA1/2 and PALB2 pathogenic variant carriers to controls after receiving platinum-based therapy and found that the overall response rate in mutation carriers was 58%, and 21% for non-mutation carriers.

Another type of chemotherapy that is effective for treating DNA damage repair-defective cancers is Poly(ADP-ribose) polymerases (PARP) inhibitors. PARPs are enzymes that are activated by DNA damage, and suppression of these enzymes can result in cell death due to the inability of the cell to fix errors in DNA. A randomized double blind, placebo-controlled study of 154 individuals with metastatic pancreatic cancer and a germline BRCA1/2 pathogenic variant showed that individuals who were treated with olaparib, a PARP inhibitor, had significantly longer progression-free survival than those treated with placebo (7.4 months v. 3.8 months), although the overall survival between groups was not significantly different. PALB2 and ATM are also involved in the DNA-damage repair pathway with BRCA1/2, and therefore treatment with PARP inhibitors in other cancer types, like prostate cancer, has been successful at reducing prostate-specific antigen (PSA) in males with castrate-resistant prostate cancer. This demonstrates the
utility of PARP inhibitors in cancer types besides breast and ovary for individuals with PALB2 or ATM pathogenic variants.

The National Comprehensive Cancer Network (NCCN) recommends that all individuals with pancreatic cancer have their tumors tested for microsatellite instability (MSI). About 13% of pancreatic tumors are mismatch repair deficient (dMMR) or MSI-high, which can be indicative of a germline pathogenic variant in a Lynch syndrome gene. These types of tumors have a high mutation burden and are eligible to receive immunotherapy like Pembrolizumab. Pembrolizumab is often used in dMMR/MSI-high colorectal cancer, and has shown to have similar response in individuals with non-colorectal cancer. Pembrolizumab is an immunotherapy that activates the immune system by binding to PD-L1, an immune system checkpoint receptor, which allows for activation of T-cells that can then go on to attack cancer cells. The immune response is stimulated by the high mutational burden in these tumors. Although limited research has been done on Pembrolizumab in individuals with PDAC, one study of 22 patients with dMMR/MSI-H pancreatic cancer, had one patient with a complete response, three patients with partial responses, and a mean duration of response of 13.4 months. In another study, those who had surgery and had a dMMR/MSI-High tumor were found to have increased survival when compared to those with MSI-Low or stable tumors (p-value =0.0057).

NCCN also recommends molecular analysis of those who have metastatic pancreatic cancer. Somatic testing of an individual’s tumor can also provide more personalized treatment options. However, there is no difference between somatic mutations in KRAS, CDKN2A, SMAD4 or TP53 in patients who have a germline mutation and those who do not. Additionally, only about half of the individuals with a germline variant in this study had a second somatic hit in their tumor, which raises questions about if the germline mutation is the cause for that individual’s pancreatic
cancer in the first place.\textsuperscript{2} One study found that performing next-generation sequencing and immunohistochemistry on pancreatic cancer tumors found a highly actionable variant in 27\% of cases, and those who had a tailored therapy based on their tumor findings had significantly longer progression-free survival (p-value=0.03).\textsuperscript{67}

2.6 Access to Genetic Testing

While genetic counseling is a growing field, the demand for genetic services and the need for clinical genetic counselors to utilize alternative service delivery models is increasing.\textsuperscript{6} Almost 50\% of genetic counselors use at least two different alternative service delivery models in their daily practice, including telephone, telemedicine and group counseling.\textsuperscript{68} Use of alternate delivery models can reduce travel distance to centers where genetic services are offered, time spent waiting for an appointment with a genetic counselor, and increase in access to genetic services.

For individuals with cancer, long wait times for an appointment can cause a barrier to the best possible care. This is especially critical for individuals with pancreatic cancer, because there is a high risk that the patient may die before genetic testing is performed. Because of the possibility for tailoring treatments based on germline mutation status, having this information early in the course of management of the disease is important. Additionally, as already discussed, having genetic testing can provide one’s family members with valuable information about their own cancer risk.

In order to make genetic testing more widely available, some institutions have developed video education for specific populations. One such study is the MAGENTA trial, which aimed to make genetic testing more accessible for women who may be at risk to develop ovarian cancer due
to a personal or family history of cancer, as the majority of those meeting guidelines for testing had not had genetic services. The success of the video education could potentially be adapted for population screening, as the field goes back and forth on population screening for BRCA1/2 and Lynch syndrome. Another study used a genetic counseling educational video in a population of women with ovarian, fallopian or peritoneal carcinoma. This study involved comparing genetic testing uptake between women who were referred to genetic counseling and women who watched the educational video on the same day. Fifty-five percent of individuals in the video group had genetic testing, while only 29% of individuals offered the genetic counseling appointment had genetic testing (p-value <0.001). Although other factors could have contributed to the different in uptake, it demonstrates that same-day video education provides a convenient way to access genetic testing services, while having to wait for another appointment significantly decreases the amount of women who have genetic testing.

2.7 Health Literacy and Other Factors Influence Genetic Testing Decision Making

A comprehensive review was conducted by Sweeny et al to determine common factors impacting testing decisions across the literature. The review found that attempts to quantitatively predict genetic testing are not as consistent as those that use qualitative measures. They also found that people are more likely to pursue genetic testing if they perceive that there are more benefits to testing than there are risks, while factors about a condition, like perceived associated risk of testing positive was not a good predictor of genetic testing. Even studies examining patient willingness to undergo the same test, for example for BRCA1/2, were discordant. This review
highlights that there is no way to predict uptake of genetic testing and this topic warrants more research.\textsuperscript{71}

A study of 584 individuals with pancreatic cancer who received genetic counseling found that younger patients, patients with a personal history of breast or gynecologic cancer or with a family history of a first degree relative with breast cancer were more likely to undergo testing (p-values = 0.019, 0.0001, 0.0085, 0.0047 respectively). Patients with chronic pancreatitis were less likely than others to undergo testing (p-value = 0.014). The researchers noted that the individual’s interest in genetic testing may be influenced by their provider.\textsuperscript{72} A study of genetic testing decision making in women at risk to have a $BRCA1/2$ mutation found that people with more education were more likely to have testing. Other factors that influenced the women’s decision making were family history of cancer and whether or not they had children.\textsuperscript{73} Researchers also found that those who perceive their chance to have a pathogenic variant are more likely to pay for genetic testing.\textsuperscript{74} Recently, Invitae started offering free germline genetic testing for individuals with pancreatic adenocarcinoma, which may remove this barrier for those who perceive their risk to have a mutation to be low.

It is well documented that roughly 36% of adults in the United States have basic or below basic health literacy.\textsuperscript{75} Poor health literacy has been linked to higher chance of hospitalization, increased prevalence and severity of chronic diseases, lower utilization of healthcare services and overall poorer health outcomes.\textsuperscript{76} The average genetic literacy level is expected to be even lower than health literacy, and presents challenges particularly to those with low literacy. A genetic literacy tool, the rapid estimate of adult literacy in genetics (REAL-G), was used to measure one’s baseline genetic literacy. This validated measure was based on the rapid estimate of adult literacy in medicine (REALM). Both the REAL-G and the REALM were given to 203 study participants.
They were asked to read a series of words, and each correctly and incorrectly pronounced word was noted. The short form of the REAL-G measure was constructed with the eight most commonly mispronounced words from the long form of the REAL-G. The REAL-G measure identified 88.2% of individuals who were found to have a 6th grade or below reading level on REALM (sensitivity 89.3; specificity 80.8%).

Identifying patients who have lower literacy is important, as patients should understand the risks and benefits of genetic testing before a test is performed. Patients with low literacy may need to be educated about genetics in a different way than a patient without low literacy. Research on educational tools for low-literacy patients illuminated a few interesting themes, including that most participants said this study was their first introduction to genetic counseling and testing. Individuals with low health literacy were more likely to have lower genetic knowledge (p-value<0.0001) and less likely to be familiar with family health history (p-value= 0.02). Interestingly, the researchers found that individuals with low health literacy thought genetic information was very important, but that family health history information was not important, indicating a disconnect in this population. Individuals with a high school education were more likely than those with a college degree to believe that genetics does not determine someone’s cancer risk (p-value <0.01). This could potentially impact health behaviors, as people who do not believe genetics contributes to cancer may take on a more active role in their health by avoiding smoking or maintaining a healthy body weight, or take the opposite approach of leaving their chances of developing cancer up to fate. Although the study did not explore if there was a difference in uptake of genetic testing between the education groups, one could infer that if a person thought genetics does not contribute to cancer risk, they would be less likely to undergo testing. These findings indicate that health literacy contributes to attitudes about importance of
genetics and family history may influence one’s willingness to have genetic testing and change their health behaviors based on those results.

2.8 Impact of Genetic Testing Results on Emotional Distress

There is conflicting evidence regarding the impact of genetic testing on emotional state, with some research suggesting disclosure of a positive result does not have any negative impact on a cancer patient, and others suggest that a positive result can lead to anxiety and depression. One study performed in a population of women with ovarian cancer identified significant levels of anxiety both before and after genetic counseling, however anxiety levels improved at 6 month follow up. This study found no differences in distress between genetic testing results (positive, negative, and variant of uncertain significance) at any time point. This indicates the higher levels of anxiety measured at the time of the genetic counseling appointment were possibly related to their recent diagnosis of cancer (average of 34 days between diagnosis and testing), rather than the genetic testing itself.82

Individuals with pancreatic cancer are facing a devastating diagnosis with poor prognosis compared to other cancer types.7 Anxiety decreases one’s quality of life, and research shows that like other cancer types, self-reported quality of life in pancreatic cancer patients is associated with survival.83,84 One measure, the Multidimensional Impact of Cancer Risk Assessment (MICRA) was developed specifically to assess emotional impact of genetic testing on patients. This survey tool has been used in many studies to measure emotional distress, uncertainty, and positive experiences after receiving genetic testing for cancer risk.85 This survey was first used in a population undergoing testing for BRCA1/2 mutations, and was able to distinguish distress,
uncertainty and positive experiences in those individuals who tested positive from those who tested negative.\textsuperscript{85}

MICRA was used in a study of individuals diagnosed with pancreatic cancer undergoing genetic testing to examine the difference distress between patients who met genetic testing criteria and those who did not, prior to the change of ASCO and NCCN guidelines. There was no difference in total MICRA scores between those who met guidelines and those who did not, and no difference in total MICRA scores between those who tested positive, negative or were found to have a variant of uncertain significance.\textsuperscript{86} Based on the limited available research, genetic testing does not appear to have an adverse impact on patients with pancreatic cancer, and therefore likely does not affect quality of life for these patients.
3.1 Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal types of cancer, with a 5-year survival rate of only 9%. Because of the non-specific symptoms like jaundice, weight loss and abdominal pain, PDAC is often not diagnosed until it is metastatic. Metastatic cancer is more difficult to treat, and cannot be cured.

The risk of PDAC is influenced by modifiable factors like smoking and alcohol intake, and non-modifiable factors, including age, sex, family history, and genetics. Regardless of family history of cancer or age at pancreatic cancer diagnosis, approximately 10% of affected individuals have a clinically actionable germline pathogenic variant. An increased risk of pancreatic cancer has been associated with High Risk Breast and Ovarian Cancer syndrome (HBOC), Lynch Syndrome, Peutz-Jeghers syndrome, Familial Atypical Multiple Mole Melanoma (FAMMM), Familial Adenomatous Polyposis, Li Fraumeni syndrome, and Hereditary Pancreatitis. In addition, some families with multiple affected family members do not have an identifiable pathogenic variant and have a diagnosis of Familial Pancreatic Cancer (FPC). Even without a germline pathogenic variant, individuals with a family history of pancreatic cancer have an increased risk of developing PDAC.

In 2018, national guidelines regarding genetic testing of individuals with PDAC changed to recommend genetic assessment and germline testing for all individuals with PDAC, regardless of family history of cancer or age of onset. Knowing germline status for individuals with pancreatic cancer can provide information about risks for family members and has potential
treatment implications. For example, the POLO study found that individuals with PDAC and a BRCA1/2 pathogenic variant who received standard of care chemotherapy had a longer period of progression-free survival when compared to the placebo group.

Screening for pancreatic cancer in the general population is currently not recommended because the risk of pancreatic cancer in the general population is low (1.6%), imaging of the pancreas is suboptimal to detect most advanced precursor lesions (PanIN-3) or small, less than 1 cm, pancreatic tumors, and an effective biomarker for pancreatic cancer is not available. However, surveillance of high-risk individuals has been shown to diagnose pancreatic cancer at an earlier stage and therefore, identification of those at increased risk is important so that appropriate surveillance measures can be pursued.

Genetic counselors are often involved in facilitating germline genetic testing. However, there is a shortage of genetic counselors, which can lead to long wait times for appointments. Because of the high mortality rate of pancreatic cancer, it is possible that patients may die before they are able to access genetic services. In addition, germline genetic testing can inform treatment decisions and provide risk information for family members. For these reasons, it is important to explore alternative service delivery models in this population to identify methods for increasing timely access to genetic specialists. Educational videos have been used in other populations to increase access to genetic education. In a study of parents’ knowledge assessment of children undergoing whole exome sequencing, no significant differences were seen in genetic or whole exome sequencing knowledge between the group that watched a video and the group that did not watch the video. The participants in this study also reported no difference in their satisfaction with education between groups. In 2005, a study of video use in cancer genetic counseling practices was conducted and found that only about 30% of genetic
counselors utilize videos to aid in their practice, and those that did said that use of an educational video increased their efficiency. However, when educational videos are used to replace genetic counseling, the psychosocial support provided by genetic counselors is no longer available to patients who are undergoing the genetic testing process, and some counselors felt worried that using a video would ultimately make them obsolete.

The purpose of this study was to evaluate the efficacy of video education for a population of individuals with pancreatic cancer. Most research that has examined knowledge following genetic education and distress following results disclosure has been completed in a population undergoing BRCA1/2 testing for breast cancer risk. As such, questionnaires assessing knowledge are not geared towards the needs of this unique population. Watching a video removes the personal relationship between a counselor and a family and may increase distress and uncertainty levels following disclosure of genetic testing results. Distress and uncertainty levels have been measured in this population after genetic counseling, but no studies in the literature have measured distress after genetic education through video in this population.

3.2 Methods

3.2.1 Participants

At the University of Pittsburgh Medical Center (UPMC), the majority of patients with newly diagnosed PDAC attend the pancreatic Multidisciplinary Clinic (MDC), also called the Pancreas Specialty Care Center. This clinic is held one day a week. In the morning, the clinic is held at Hillman Cancer Center, and in the afternoon it is held in the Digestive Disorders Center at
Presbyterian Hospital. Patients are scheduled by the clinic coordinator based on their location, time and physician preference. They may also be scheduled around other appointments, like imaging scans to further define disease stage. Surgeons, medical oncologists, pain management specialists, dieticians and clinical trials staff are available at both locations. Patients seen in the morning MDC at Hillman Cancer Center were assigned to the traditional genetic counseling group, and the patients seen in the MDC in the afternoon at Presbyterian Hospital were assigned to the video group. The University of Pittsburgh Institutional Review Board approved this study (STUDY19040249) (Appendix A.5).

3.2.2 Eligibility Criteria

Patients were deemed eligible for the study if they were seen in the MDC and had histologically confirmed newly diagnosed pancreatic ductal adenocarcinoma, regardless of age at diagnosis, gender, or personal or family history of cancer. Participants were excluded from the study if they had previously undergone panel testing for hereditary cancer. Participants with a known family history of a germline pathogenic variant were not excluded as long as they have not had testing for the pathogenic variant themselves.

3.2.3 Recruitment

Potential participants in both the traditional genetic counseling group and the video education group were approached about the study at their MDC appointment before the genetic education took place. The study was explained to all potential participants, questions were answered, and patients who agreed to participate in the study provided informed consent.
3.2.4 Instruments

In this study, the REAL-G, Pancreatic Genetic Knowledge Questionnaire and MICRA instruments were used to assess participants’ genetic literacy, pancreatic cancer genetic knowledge and distress and uncertainty following the return of genetic testing results, respectively. The REAL-G and MICRA instruments are validated questionnaires, while the Knowledge Questionnaire was designed specifically for this study. The REAL-G was administered in person. The Knowledge Questionnaire and MICRA were administered orally, with the coordinator reading the measure aloud for the participant.

3.2.4.1 REAL-G

The Rapid Estimate of Adult Literacy short form was adapted from the REAL-G long form and found to be an efficient assessment of genetic literacy. This tool was created to measure an individual’s familiarity with genetics. For the purpose of this study, the participant was asked to read a list of words related to genetics. The investigator administering the instrument also had a copy of the words and kept track as the participant read them aloud. Participants were instructed to read the words at their own pace and were made aware that they could skip over any word they have trouble pronouncing.

Participants were asked to attempt to pronounce words related to genetics to the best of their abilities. These words are “genetic,” “sporadic,” “mutation,” “variation,” “chromosome,” “hereditary,” “abnormality,” and “susceptibility”. Words that the participant pronounced correctly were marked with a “+”, and those that were pronounced incorrectly, or that the participant skipped, were marked with a “-”. A total of 3 or more missed or skipped words equates to a 6th grade or below reading literacy level.
3.2.4.2 Knowledge Questionnaire

The Knowledge Questionnaire was designed for this specific patient population, as there are no published questionnaires in the literature that would accomplish the specific aims of the study. The questionnaire was designed to elicit knowledge that is addressed in genetic counseling sessions for patients with PDAC. Two experienced genetic counselors who specialize in gastrointestinal cancer genetics were involved in the construction of the questionnaire. In order to not place significant burden on participants, the questionnaire was designed to be short and succinct. The questionnaire was administered verbally at two time points, the first time in person immediately following genetic education and the second time over the phone two weeks following return of genetic testing results.

The knowledge questionnaire consists of 7 questions that are answered in a true/false format. Each question has equal weight and scores out of 7 were recorded for both time points.

3.2.4.3 MICRA

The Multidimensional Impact of Cancer Risk Assessment (MICRA) measures the emotional impact of disclosure of cancer genetic testing results. The tool assesses distress, uncertainty and positive experiences following disclosure of genetic testing results. It assesses participants’ attitudes regarding the genetic counseling and testing process and risk management. The MICRA can be used to compare groups based on their genetic test results or based on the type of genetics education they received prior to genetic testing. This instrument was administered once over the phone, 2 weeks after genetic testing results were returned.

The MICRA has 25 questions that assess the frequency of uncertainty, distress and positive experiences regarding genetic testing in the last week. There are four response options for each question; never (0 points), rarely (1 point), sometimes (3 points) and often (5 points). There are
six items that fall into the “distress” distress subscale, for a maximum score of 30 points. There are nine items in the “uncertainty” subscale, for a maximum of 45 points. There are 4 items in the “positive experiences” category that are reverse scored, such that “never” is 5 points, and “often” is 0 points. The maximum possible score for positive experiences subscale is 20. A MICRA score is considered “high” if it is one standard deviation above the mean or higher.\textsuperscript{85}

3.2.5 Study Protocol

The research team was comprised of genetic counselors, a gastroenterologist, surgical oncologists, medical oncologists, research coordinators and a genetic counseling student who facilitated the enrollment process and administered follow up questionnaires.

Patients in the MDC were approached about the study. Individuals were informed about the study and were given the opportunity to ask questions. Patients who declined participation in this research study were still offered genetic education and the option of having genetic testing during their appointment in the MDC or provided contact information for the Hereditary GI Tumor Program if they were interested in pursuing genetic testing in the future.

During the first timepoint, participants provided informed consent and the genetic literacy questionnaire was administered. In the traditional education group, the genetic counselor was not aware of the score of the genetic literacy assessment prior to meeting with the patient as to avoid any bias or alteration of counseling. After the education, the knowledge questionnaire was administered to the participant orally and the results were recorded (Figure 1). The assessments were given in the presence of any family members that the participant brought with them to the appointment, and they were instructed not to aid the participant in answering the questions. The
participant was also instructed to direct any questions regarding the counseling process to the genetic counselor or a member of their oncology team.

The traditional education consisted of collection of a pedigree, education about hereditary pancreatic cancer, and discussion of the risks, benefits, and result outcomes of genetic testing. The genetic counseling session was abbreviated. The time spent with the participants was not recorded, however it was at least 15 minutes and included completion of paperwork, like testing consent forms and release of information to family members, and discussing a plan for results disclosure. The video education involved watching a 5-minute video designed and developed by licensed and certified genetic counselors who specialize in gastrointestinal cancer genetics. This video was a narrated PowerPoint slide deck specially tailored to individuals with pancreatic cancer, although it was more general information. Oncology teams were provided with talking points on specifics of the test that was being offered and gave the patient a consent form to review and sign. A pedigree was not collected for individuals who watched the video.

Participants who elected to undergo genetic testing were offered testing through Invitae’s Detect study, which waives the price of the genetic test for individuals with PDAC. As part of the Detect study, all participants who had genetic testing received a panel containing 86 genes related to increased risk of pancreatic and other cancers. A complete list of analyzed genes can be found in Appendix C.

Results were returned to the participant when they became available. The participants who had traditional genetic education received their results from their genetic counselor over the phone. Participants who had the video education received their genetic testing results from a member of their oncology team who was trained by the genetic counselors to return results. Anyone who received genetic testing following the video education and was found to have a pathogenic variant
were referred to a genetic counselor for a more detailed discussion (Figure 2). Participants in the video education group whose families met the designation of FPC were told that their family members may want to meet with a genetic counselor to discuss their risk.

Two weeks after their genetic testing results were returned (Timepoint 2), participants were contacted via telephone. At this time, participants were reminded of their participation in the study and were asked if they would be willing to answer some follow-up questions. If the participant agreed, the seven true/false questions on the knowledge questionnaire were read aloud and the participant’s responses were recorded. Then, the MICRA was administered and the responses were recorded. At this time, the participants were thanked for their participation in the study and were told that their participation in the study was complete, except if they were in the video group and were found to have a pathogenic variant. These participants were asked to answer the knowledge questionnaire one additional time in clinic after their discussion with a genetic counselor. At this time, the participants were thanked for their participation and told that their involvement in the study was complete (Figure 1).
Figure 1 Protocol Workflow
3.2.6 Data Analysis

The data was assessed for normality. For the MICRA, all subscales were assessed individually for normality. A Chi Square test was used to determine if genetic literacy differed between groups. A Wilcoxon Sum-Rank test was performed to determine if there is a relationship between genetic literacy and score on knowledge questionnaire at timepoint 1, and knowledge questionnaire and MICRA scores at timepoint 2. A Wilcoxon sign-rank test was used to compare
genetic knowledge score over time. The statistical analysis was performed in Microsoft Office Excel and STATA (Stata Corp 2015). P values were considered significant when they were \( \leq 0.05 \). Outputs from STATA can be found in Appendix B.

3.3 Results

Participants were recruited between January 8 and March 4, 2020, and a total of 14 participants consented to be in the pilot study. All participants had a current diagnosis of pancreatic adenocarcinoma. Nine participants were enrolled into the video group, and five participants were enrolled in the traditional genetic counseling group. Each participant, except for UPT11, was followed at least three weeks following enrollment. UPT11 elected not to have genetic testing following education, so he was not contacted for data at the second timepoint.

3.3.1 Demographics

Of the 14 participants, five (35.7%) were female and all patients were Caucasian. Participants ranged from age 41 to 83 years old, with a mean age of diagnosis of pancreatic cancer at 65.1 (± 2.7 years). In the traditional genetic counseling group, 60% (3) of the participants were women. The average age of the traditional genetic counseling group was 67.0 (± 4.16), ranging from 60 to 83. The video group was comprised of 22.2% females, and the mean age at diagnosis was 64.0 (± 3.64), ranging from age 41 to 82 (Table 1). There were no significant differences between age or sex between groups (p-value = 0.9467; 0.1732 respectively). All patients met NCCN criteria for genetic testing based on their personal history of PDAC. The mean number of
days between diagnosis and enrollment into the study was 8.71 (± 1.10), which was not significantly different between education groups (p-value = 0.1545).

<table>
<thead>
<tr>
<th>Table 1 Demographics</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
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<td></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Range</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

**3.3.2 Baseline Measure of Genetic Literacy**

Baseline measurement of genetic literacy was evaluated using a modified REAL-G tool. The administered measure was inadvertently missing the word “chromosome.” As such, participants UPT7 and UPT10, who missed two words each, were excluded from analysis, because their literacy level could have changed with the addition of “chromosome”. Both of these participants were in the video education group. The statistical analysis was completed on the 12 remaining participants.

In total, four out of 12 participants (33.3%) were found to have 6th grade or below literacy level. Two participants in each group had low literacy, who accounted for 40% of the traditional education group and 28.6% of the video education group (Table 2). The literacy levels between education groups was found to be not significant (p-value = 0.5724).
### Table 2 Genetic Literacy

<table>
<thead>
<tr>
<th>Literacy Group</th>
<th>Traditional Education</th>
<th>Video Education</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=5</td>
<td>n=7</td>
<td>n=12</td>
</tr>
<tr>
<td>6&lt;sup&gt;th&lt;/sup&gt; Grade or Below</td>
<td>40.0% (2)</td>
<td>28.6% (2)</td>
<td>33.3% (4)</td>
</tr>
<tr>
<td>Above 6&lt;sup&gt;th&lt;/sup&gt; Grade</td>
<td>60.0% (3)</td>
<td>71.4% (5)</td>
<td>66.7% (8)</td>
</tr>
</tbody>
</table>

### 3.3.3 Genetic Knowledge in Relation to Literacy

Baseline measurement of genetic knowledge in regards to pancreatic cancer was measured using the designed knowledge questionnaire. The mean number of questions answered correctly following education was 6.0 (± 0.30) out of a possible 7. On average, those with 6<sup>th</sup> grade or below literacy scored 5.75 (± 0.75) out of 7, and the group with higher literacy scored 6.13 (± 0.30), though this difference was not significant (p-value = 0.7206). In the traditional education group, regardless of baseline genetic literacy, the average number of questions answered correctly was 6.0. In the video education group, those with low literacy had a mean score of 5.5 (± 1.50), while those with above 6<sup>th</sup> grade literacy had a mean score of 6.2 (± 0.37) (Table 3). Overall, there was no significant difference between scores on the knowledge questionnaire at timepoint 1 based on education group (p-value = 0.9313). Scores on the knowledge questionnaire from the video education group did not significantly differ based on literacy level (p-value= 0.6849).

### Table 3 Average Knowledge Score by Literacy Level and Education Group

<table>
<thead>
<tr>
<th>Literacy Group</th>
<th>Traditional Education</th>
<th>Video Education</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>6&lt;sup&gt;th&lt;/sup&gt; Grade or below</td>
<td>6</td>
<td>5.5</td>
<td>5.75</td>
</tr>
<tr>
<td>Above 6&lt;sup&gt;th&lt;/sup&gt; Grade</td>
<td>6</td>
<td>6.2</td>
<td>6.13</td>
</tr>
</tbody>
</table>

Mean score on the knowledge questionnaire out of 7 total possible points.
3.3.4 Genetic Knowledge Across Timepoints

In addition to participant UPT11, who did not have genetic testing, three participants were not able to be reached before this data was analyzed. Therefore, only 10 participants’ information was analyzed across time points.

On average, timepoint 2 was 27.80 (± 2.31) days (range 21-40) from genetic testing. This is slightly less than four weeks between questionnaires. The number of days between timepoints 1 and 2 was significantly different in the groups, with those in the genetic counseling group being contacted on average 10.8 days before those in the video group (p-value= 0.0109).

The mean knowledge score at timepoint 2 was 5.45 out of 7, or 0.78 (± 0.43) points lower when compared to timepoint 1. Two participants, UPT6 and UPT14, increased their score at the second timepoint, although UPT14 disclosed that he didn’t remember the answers and was guessing on some of the questions. Another participant, UPT1, had no change in her score over time. All other participants had a decrease in score between timepoints. When comparing knowledge over time, there was a decrease in the number of questions correct, however this was not significant overall (p-value= 0.1682). Those with low literacy were not found to have a significantly lower score at timepoint 2 than those without low literacy (p-value= 0.7835).

At timepoint 2, the difference between knowledge scores was not significant by education group (p-value= 0.3160). The change in score between timepoints 1 and 2 for the video education group was an average of -1.0 (± 0.70) (p-value= 0.1573). The change in score between timepoints 1 and 2 for the traditional genetic counseling group was an average of -0.2 (± 0.58) (p-value= 0.5791) (Table 4).
Table 4 Knowledge Over Time

<table>
<thead>
<tr>
<th>Education</th>
<th>Average Change in Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>0.20 (± 0.58)</td>
</tr>
<tr>
<td>Video</td>
<td>-1.00 (± 0.70)</td>
</tr>
</tbody>
</table>

Mean difference in scores out of 7 over time.

3.3.5 MICRA

The MICRA instrument was administered via telephone two weeks following the return of genetic testing results for the 10 individuals who were contacted for timepoint 2.

The average total MICRA score was 25.50 (± 4.39), and the median score was 25 (IQR, 13-37.25). No significant difference in overall MICRA scores was observed between education groups (p-value= 0.6742). The mean distress subscale score was 5.60 (± 1.70). There was no significant difference in distress scores between education groups (p-value= 0.6752). The mean uncertainty score was 14.50 (± 2.89). There was no significant difference in uncertainty score between education groups (p-value= 0.2477). The mean positive experiences score was 3.80 (± 1.06). There was no significant difference in positive experiences between education groups (p-value= 0.8299).

A score of 1 standard deviation above the mean is defined as a high score. In this study, a score of 38.69 or higher is considered a high MICRA score. One participant, UPT7, reported high emotional distress levels.

Participants were also asked if they regretted having genetic testing on the MICRA instrument. One participant responded that he rarely regretted having testing, and all other participants indicated that they have never regretted their decision to have genetic testing.
3.3.6 Genetic Testing Results

Of the 13 participants who underwent genetic testing, 12 participants had results returned by Invitae at the time of data analysis. Four of these 12 participants were found to carry a pathogenic variant. Pathogenic variants were identified in \textit{ATM}, \textit{APC} (p.I1307K), \textit{BLM} (heterozygous) and \textit{MUTYH} (heterozygous). The pathogenic variant in \textit{ATM} was considered to be clinically actionable for the participant. Only one participant out of the 12 (8.3\%) with results had a pathogenic variant in a gene associated with PDAC. Six participants had at least one variant of uncertain significance (VUS) identified. VUS were identified in \textit{APC}, \textit{BRCA1}, \textit{CEBPA}, \textit{MET}, \textit{NF2}, \textit{POLE} and \textit{RECQL4}. Four participants had no pathogenic variants or VUS identified in any of the 86 genes tested.

3.4 Discussion

Recent revisions to national guidelines recommend genetic testing for all individuals with pancreatic ductal adenocarcinoma (PDAC), as an estimated 10\% of pancreatic cancers are due to a germline pathogenic variant.\textsuperscript{1,4,5} Video education was implemented at UPMC in order to expand genetic testing availability to more patients. The goal of this pilot study was to assess efficacy of video education for patients with PDAC, both from a knowledge retention standpoint and from a psychosocial standpoint. Individuals who underwent video education were compared to individuals who met with a genetic counselor. To our knowledge, this pilot study is the first report assessing participant knowledge and emotional distress following genetic education by video.
Of the 12 participants whose genetic testing results were returned by the time of data analysis, one participant (8.3%) was found to have a pathogenic variant in a \textit{ATM}, which is related to an increased risk for pancreatic cancer.\textsuperscript{1} The rate of clinically actionable pathogenic variants in this pilot study is similar to that of other research studies.\textsuperscript{1,4} Three other pathogenic variants were identified in study participants, although these are not related to an increased risk of PDAC. Pathogenic variants in \textit{MUTYH} and \textit{BLM} are associated with autosomal recessive inherited predisposition syndromes. Because each participant only had one pathogenic variant identified, they are carriers for these conditions and do not have the syndrome themselves. An additional participant had a pathogenic variant identified in \textit{APC}. The variant detected is a founder mutation called p.I1307K, which does not result in the typical Familial Adenomatous Polyposis phenotype, but rather a moderately increased risk for colon cancer. Some research suggests that males with this specific pathogenic variant have an increased risk of developing pancreatic cancer.\textsuperscript{91} The participant in which this pathogenic variant was a male.

In order to adjust for any differences that baseline genetics knowledge might have had on post-education knowledge, the participants were asked to complete a baseline measure of genetic literacy. The REAL-G measure used in this study is a validated measure, and is able to predict general health literacy.\textsuperscript{77} Research has suggested that health literacy is the best predictor of health outcomes.\textsuperscript{76} In this pilot study, one-third (33%) of participants were found to have low genetic literacy, which is defined as a 6\textsuperscript{th} grade literacy level or below. This is similar to larger research studies that report a basic or below basic literacy rate of 36% in the United States.\textsuperscript{75} Analysis did not identify a difference in genetic literacy between the group that received traditional genetic education and those who watched the video. This is what we expected, as patients are not
scheduled to either clinic based on any personal or clinical characteristics, but on their preference for appointment time and location.

We anticipated that performance on the knowledge questionnaire would be significantly associated with genetic literacy. Individuals found to have a 6th grade or below literacy level answered an average of 5.75 (± 0.75) out of 7 questions correctly, while the group with higher literacy scored 6.13 (± 0.30) out of 7. Although a difference in performance on the knowledge questionnaire was observed between literacy levels, it is not significant. It is possible that in a larger sample this would reach significance.

We hypothesized that participants in the video group would not score differently than those in the genetic counseling group on the knowledge questionnaire, as both groups were presented with the same information, just in different formats. Baseline genetic literacy level had no impact on the knowledge score for the participants in the traditional education group, as the average number of correctly answered questions in this group was 6 regardless of literacy level. The number of questions answered correctly differed by literacy level for the group who watched the educational video, although this difference is not significant. Should this finding reach significance with a larger sample size, it may be that the combination of baseline literacy and education delivery mode, rather than education delivery mode alone, is a better predictor of knowledge retention. If literacy level is able to predict knowledge score in the video education group but not the genetic counseling group, this could be due to the manner in which the genetic counselors are presenting the information. Although the genetic counselors were not aware of a participant’s genetic literacy level before education, they are trained to assess a patient’s understanding of information and adjust their counseling accordingly. This provides an opportunity for future research. If, in a larger sample size, literacy level is predictive of knowledge
retention for those in the video education group, then identification of patients with low literacy is critical for them to receive the most appropriate care. Referring patients with low genetic literacy to a genetic counselor could increase their understanding of key points regarding genetic testing. In contrast, patients with higher literacy levels may be more appropriate candidates for an educational video, which would allow them to receive the relevant genetic information without a genetic counseling referral. This could potentially save both genetic counselors’ and patients’ time; however, more data is needed to make a determination on this.

There was a significant difference in the amount of time between timepoints 1 and 2 in the two groups, which could potentially influence scores on the second timepoint and MICRA scores. However, we are not sure if this is a difference in the amount of time for clinicians to return genetic testing results or until the coordinator found out from the oncology teams that results had been returned. This difference in time could exist for a few reasons, all of which are logistical as oncology teams become accustomed to the new procedures. The main difference is that genetic counselors have experience in interpreting results and an existing infrastructure in place for contacting patients and documenting results in the electronic medical record. This made it easy for the coordinator to find out about return of genetic testing results for tracking purposes. Secondly, oncologists ordering the testing for participants in the video group were harder to ascertain status updates from, and often did not document results phone calls in the electronic medical record. As ordering genetic testing and giving results back to patients becomes more routine, this difference may become non-significant.

We expected that participants would have lower knowledge scores at the second time point, because information learned in a stressful time is harder to retain. Although participants generally performed poorer on the knowledge questionnaire at the second timepoint compared to
the first, this change was not significant. Furthermore, the difference in knowledge retention between the two education groups was not significant, despite the significantly longer amount of time between timepoints for the video education group. This suggests that the main points of genetic education are retained a month after education regardless of the mode of delivery.

Research has shown that the majority of individuals undergoing genetic testing do not experience high levels of anxiety and for this reason, we expected that there would not be a significant difference in levels of emotional distress between the two groups. Most of the questions on the MICRA questionnaire assess participants’ feelings about their results, and not about their experience with genetic education. Future research could explore participants’ opinions of the video to assess emotional distress related to the education experience, rather than emotional distress related to their results. When distress measures were evaluated, scores on the MICRA instrument and all of the subscales did not vary by education group. It is encouraging that individuals who did not speak to a genetic counselor were not more distressed or uncertain about their results in comparison to the group that spoke to a genetic counselor. Because of the limited number of participants in the study, differences between result type (positive, negative or variant of uncertain significance) were not able to be analyzed, however in another study utilizing MICRA in a population of pancreatic cancer patients, there was no observed difference in emotional distress seen between result types.

Another study performed in a similar population reported a median MICRA score of 16 (IQR, 11-23), which differs from the median score of 25 (IQR, 13-37.25) in this pilot study. It is possible that this difference is related to when participants completed the assessment of emotional distress about their results. In this pilot study, participants completed the MICRA on average 27.80 days after genetic testing, while in the Peters et al study, the MICRA was completed
Research shows that distress about genetic testing results decreases over time and it is possible that if we asked participants to complete the MICRA again in a few months, the results of this study would be more consistent with other research studies.

One participant, UPT7, had a high MICRA score, as defined by a score of 1 or more standard deviations above the mean. This high score could be due to a number of factors that could not be evaluated at this time due to the small sample size. For example, the type of test result may influence distress and uncertainty following genetic testing. It is reasonable to speculate that a person with a positive result would experience a higher level of distress or uncertainty than those with negative results. However, UPT7 was negative for all 86 genes analyzed. Other factors that could influence the MICRA score are age at diagnosis, prior history of cancer, or family history of cancer. It is also possible that the participant had a difficult time distinguishing distress caused by genetic testing from distress due to their cancer diagnosis. A larger sample size is needed in order to stratify MICRA analysis by these additional variables that could contribute to distress.

3.4.1 Study Limitations and Future Directions

The results from this pilot study demonstrate the feasibility of this project and warrant additional exploration into the use of video education to increase the access to genetic information, not only for patients with pancreatic cancer, but potentially with other cancer types. Although the absence of observed significant differences between the traditional genetic counseling group and the video education is encouraging, the available data does not prove that the two groups are not different; due to the small cohort in the study, conclusions are limited and more data needs to be collected to fully understand the efficacy of video education as a method for delivery of genetic
Performing this study with additional participants could provide more robust data and further illuminate the findings of this pilot.

We assigned participants to either the video group or the traditional genetic counseling group based on appointment location. Because participants were not randomized to either arm by the study team, it is possible that the groups are different from one another. For example, sometimes individuals who need to have imaging to determine if their cancer is metastatic will be scheduled for the afternoon clinic so their staging studies can be completed in the morning, prior to their meeting with the oncology team. Additionally, it is possible that the time of day or location of the appointment could also have an impact on patients’ willingness to enroll in the study, or participants’ scores on the knowledge questionnaire.

The conclusions of this pilot study are limited by the small sample size. The study was designed to remain open until 200 participants, or 100 in each education group, have been enrolled. At the current rate of recruitment, this study is expected to continue until the end of 2021. Additionally, the two groups did not recruit at the same rate. For the pilot study, the video group had 9 participants, and the counseling group had 5 participants. This was expected, and can be largely explained by the fact that more patients are typically scheduled to have their MDC appointments in the afternoon.

All of the participants in this pilot study identify as Caucasian and only 35.7% were female, which is not representative of the general population of people who are diagnosed with pancreatic cancer. Due to this, the results are not generalizable to a larger population and recruitment should continue until the study sample is more representative of the greater Pittsburgh population with pancreatic cancer.
A larger study would also allow researchers to stratify data by genetic testing results, which may influence knowledge at timepoint two and scores on the MICRA analysis. One hypothesis is that participants with positive genetic testing results could have done more research on their own or received more education from providers following return of a positive result, as compared to those with a negative or VUS result. Additionally, genetic carrier status may influence distress scores on MICRA, and VUS could potentially cause more uncertainty. Because this study only examined the utility of the educational video in individuals with pancreatic cancer, conclusions cannot be made regarding utility of a video in other populations.

Additionally, there may be a lower than expected number of participants because of the time they were approached for the study. The MDC visits are typically the first visit newly diagnosed patients have with an oncologist, and the patient and family are understandably preoccupied with learning about their treatment plan and prognosis. Approaching potential participants at this stressful time could have limited the number of participants who agreed to enroll in the study. This could also cause some biases in the data, because the distress levels in people who agree to be in the study may be different when compared to those who decline to participate. No data were collected on the patients who declined to participate in the study. Obtaining information on these individuals, could provide researchers with more information about obstacles to recruitment, and therefore lead to increased enrollment in the future.

Another limitation of the study was that participants may have had difficulty distinguishing between distress and uncertainty related to their pancreatic cancer diagnosis and that related to their genetic testing results. In addition, the MICRA was initially intended to be self-administered, rather than over the phone. Altering the delivery of the measure could alter results.
Participants in the video group had their results returned by a member of their oncology team, rather than a genetic counselor. Although the oncology team members were trained to return results and were able to consult with genetic counselors before disclosing the results to the participants, it is possible that the results disclosure process differed from the genetic counseling disclosure process. In addition, knowing when the oncologists returned the participants’ results was difficult to ascertain, so some participants may have been contacted for timepoint 2 more than 2 weeks after their results were disclosed, which could potentially alter their knowledge and MICRA results by giving them more time to become accustomed to their results or perhaps doing more research on their own.

There are a number of options for future research. One would be to assess patient’s attitudes related to genetic testing in order to learn more about why some patients pursue genetic testing and others do not. This could provide researchers and clinicians with ideas about when and how to approach a conversation about genetic testing. If patients indicate that thinking about genetics at their initial oncology appointment is too stressful, researchers could try consenting individuals at a different time point in their cancer treatment to potentially increase knowledge questionnaire scores or decrease MICRA scores, while not limiting patients’ access to genetic services. It would also be interesting to investigate how the genetic testing results are utilized, both by the oncology team and by family members. This research would provide more information about treatment decisions based on results and cascade testing uptake, which are the benefits of performing genetic testing in this patient population. Additionally, due to the high levels of distress and uncertainty seen in the participants as indicated by their MICRA scores, researching strategies to reduce these emotional states could be useful. Further research aimed at exploring the literacy difference seen in the video education group could also provide a potential triage
strategy for patients in the future. Lastly, evaluating oncology teams’ comfortability with discussing genetic testing and disclosing genetic testing results would allow researchers to assess the need for continuing education.

In theory, one objection to video education is that it is not sufficient for informed consent. However, the most important reason for these individuals to have genetic testing is to inform treatment decisions, which could affect outcomes for these patients. Additionally, these individuals will likely not be needing to undergo any surveillance for other cancer types they may be at risk for because of the poor prognosis of pancreatic cancer. Given that the main reason for genetic testing is to inform treatment decisions and not prevent future cancers in the patient, we feel that the video education is sufficient counseling for these patients. If an individual is found to have a pathogenic variant, their family members are encouraged to make an appointment with a genetic counselor for a more detailed and personalized discussion of testing and surveillance of cancers associated with that finding. Because of the unique characteristics of this population, a short video explaining the risks and benefits of genetic testing is not doing a disservice to individuals with pancreatic cancer.

3.5 Conclusion

This research is the first report of genetic knowledge evaluation in individuals with pancreatic cancer, and the first report of evaluation of genetic knowledge following video education in comparison to traditional genetic counseling. Due to the small sample size, we failed to reject the null hypothesis as no significant differences were seen in knowledge or distress between the two education groups. Differences between knowledge was observed among those
who watched the video, with those having lower literacy scoring lower than those with high literacy and all literacy levels who had traditional genetic counseling, although these differences were not significant. There were no significant differences in scores on the knowledge questionnaire or on the MICRA between education groups, suggesting that the video is an effective educational tool and does not cause undue distress on participants. More research on these findings in a larger study is warranted to further elucidate these observations and determine the utility of video education and to inform potential genetic education initiatives for this population. This pilot study demonstrates the feasibility of this study design for this patient population.
4.0 Relevance to Genetic Counseling and Public Health

This pilot study aimed to explore the effects of an educational video for individuals with pancreatic cancer who are offered the option of genetic testing. This video was compared to traditional genetic counseling, and differences in knowledge and distress levels were compared in order to accomplish the study aims.

This research study has implications for genetic counseling. Genetic counseling aims to help people understand the genetic testing process and the medical and psychological implications of a test result for themselves and their family. In direct patient care, there is a shortage of genetic counselors, and because of this, alternative service delivery models have been explored, including telephone counseling, telegenetics services, and group counseling for specific indications, like advanced maternal age in a prenatal setting. Video education is a service model that is becoming more popular, and has been used by other oncology groups to increase referrals and access to genetic services.

This research explored the knowledge that patients attain during genetic education. Knowledge following genetic services has been explored in other disease types, but never for this specific population. Patients with pancreatic cancer have unique needs due to the lethality of the disease, which could understandably distract individuals from retaining much of the information given to them by healthcare providers. By creating a tool that addresses major concepts that genetic counselors hope patients with pancreatic cancer take away from a session, researchers were able to quantify patient knowledge and identify areas of a counseling session that can be improved upon. In addition, performing research on emotional distress and uncertainty provides counselors
with information about the specific emotional needs that this patient population is facing, and how genetic can tailor their services to better support these individuals and their families.

In addition to its relevance to the field of genetic counseling, this study also has implications for public health. One of the essential functions of public health is to assess a community’s needs. Following the publishing of new guidelines, all individuals with pancreatic cancer are recommended to have a genetic evaluation. At UPMC, not all patients with PDAC were being referred to genetic counseling services, and even among those that were referred, not all ended up scheduling or keeping an appointment. With the development of the educational video, patients can receive genetic information at their first appointment in the Pancreas Specialty Care Clinic. The study provides researchers a chance to evaluate the utility of the video to educate patients about genetic services, to see whether it is a useful alternate service delivery model that could be used in this population. Continuing research on alternative service delivery models, like videos, in this population is important in order to best care for patients with this diagnosis.

Assurance is another core function of a public health. One of the ways assurance can be addressed is by evaluating resources currently available. By assessing knowledge acquisition and retention after education as well as evaluating emotional distress, the efficacy of the video can be compared to traditional genetic counseling. Given the psychosocial challenges faced by patients with pancreatic cancer, it is important to determine whether educational videos cause patients more distress. By evaluating distress levels in pancreatic cancer patients undergoing genetic testing, researchers may be able to learn more about general emotional health throughout their diagnosis and treatment. Addressing emotional distress during a cancer treatment is often not the main focus, however mental health resources for individuals should be an aspect of care, as evidence shows anxiety and depression worsens outcomes. More research on this could prompt modification
of educational videos to include some psychosocial resources that patients have access to during a traditional genetic counseling session.

This pilot study showed that the video developed for this specific population is an effective way of educating patients about genetic testing and does not cause undue distress. Although the conclusions from study are limited by the small number of participants, they suggest that patients are accepting of alternate technology use in their care. This study provides valuable information about participants’ knowledge retention from genetic counseling sessions and their emotional distress following return of genetic testing results. Additionally, it shows that implementation of video education is an effective way to make genetic information more accessible to patients with pancreatic cancer. This study is valuable to the fields of genetic counseling and public health, and provides information to guide future research endeavors.
Appendix A Measurements, Consent for Protocol, IRB Approval Letter
A.1 Rapid Estimate of Adult Literacy - Genetics (REAL-G)

REAL-G Short Form

You can quickly determine your patient’s genetic literacy with this oral reading and recognition test, known as the Rapid Estimate of Adult Literacy in Genetics (REAL-G). It measures a patient’s ability to pronounce 8 words used frequently in genetics. To use REAL-G, follow these 5 steps:

1. Give the patient a copy of the following list of words. (Keep a copy for yourself)

   Genetic
   Sporadic
   Mutation
   Variation
   Chromosome
   Hereditary
   Abnormality
   Susceptibility

2. As the patient to read aloud as many words as they can, beginning with the first word. When they come to a word they cannot read, tell them to do the best they can or say “blank,” and then go on to the next word on the list.

   If the patient takes longer than five seconds to read a word, prompt them to move on by saying “blank,” and pointing to the next word on the list. If the patient begins to miss every word, as her to pronounce only those words they know.

3. On your copy of the lists, keep score of the patient’s answers. Next to each correctly pronounced word, write a plus sign (+). After each word that was not attempted or was mispronounced, write a minus sign (-).

4. This total is the patient’s raw score.

5. 3 or more missed words equates to a 6th grade or below reading level.


REAL-G Test

Please read each word below out loud to the best of your ability. If you are not sure how to say a word, you can say “blank” and skip to the next word.

Genetic
Sporadic
Mutation
Variation
Chromosome
Hereditary
Abnormality
Susceptibility
### A.2 Pancreatic Cancer Genetics Knowledge Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Please answer all items even if you are unsure of the answer.</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>About 20% of people with pancreatic cancer have a mutation, or harmful change, in a gene that increases their risk for pancreatic cancer.</td>
<td></td>
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<tr>
<td>2</td>
<td>When a gene associated with pancreatic cancer is doing its job, it helps prevent cancer from forming.</td>
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<tr>
<td>3</td>
<td>Genetic testing looks for mutations, or harmful changes, in genes.</td>
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<tr>
<td>4</td>
<td>My doctors may be able to use genetic testing results in my pancreatic cancer treatment.</td>
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<tr>
<td>5</td>
<td>If I have a mutation in a pancreatic cancer gene, my family members should consider genetic testing.</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>Genetic testing for pancreatic cancer involves looking for a mutation in only one gene.</td>
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<tr>
<td>7</td>
<td>All people who have a pancreatic cancer gene mutation will get pancreatic cancer.</td>
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</table>
The Multidimensional Impact of Cancer Risk Assessment (MICRA) Questionnaire

The questions below are about some specific responses you may have had after receiving your genetic test results. Please answer every question in Section 1, regardless of whether you were given a positive or negative test result. Please indicate whether you have experienced each statement never, rarely, sometimes, or often in the past week, by circling the corresponding number.

### Section 1

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling upset about my test result</td>
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<tr>
<td>2. Feeling sad about my test result</td>
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<tr>
<td>3. Feeling anxious or nervous about my test result</td>
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<td>4. Feeling guilty about my test result</td>
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<td>5. Feeling relieved about my test result</td>
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<tr>
<td>6. Feeling happy about my test result</td>
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<td>7. Feeling a loss of control</td>
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<tr>
<td>8. Having problems enjoying life because of my test result</td>
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<tr>
<td>9. Worrying about my risk of getting cancer (or getting cancer again if you have ever been diagnosed with cancer)</td>
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<tr>
<td>10. Being uncertain about what my test result means about my cancer risk</td>
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<tr>
<td>11. Being uncertain about what my test result means for my child(ren) and/or family's cancer risk</td>
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<tr>
<td>12. Having difficulty making decisions about cancer screening or prevention (e.g., having preventive surgery or getting medical tests done)</td>
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<tr>
<td>13. Understanding clearly my choices for cancer prevention or early detection</td>
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<tr>
<td>14. Feeling frustrated that there are no definite cancer prevention guidelines for me</td>
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<td>15. Thinking about my test results has affected my work or family life.</td>
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<td>16. Feeling concerned about how my test results will affect my insurance status</td>
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<tr>
<td>17. Having difficulty talking about my test results with family members</td>
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<tr>
<td>18. Feeling that my family has been supportive during the genetic counseling and testing process</td>
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<td>19. Feeling satisfied with family communication about my genetic test result</td>
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<tr>
<td>20. Worrying that the genetic counseling and testing process has brought about conflict within my family</td>
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<tr>
<td>21. Feeling regret about getting my test results</td>
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</tr>
</tbody>
</table>

### Section 2

If you have children, regardless of your test result, please answer Questions 22 and 23. Otherwise, please go to Section 3.

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. Feeling guilty about possibly passing on the disease risk to my child(ren)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Feeling guilty about possibly passing on the disease risk to my child(ren)</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Section 3

If you currently have cancer, or have had it in the past, please answer Questions 24 and 25. Otherwise, please check this box □. You are finished with this questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>24. Feeling that the genetic test result has made it harder to cope with my cancer</td>
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</tr>
<tr>
<td>25. Feeling that the genetic test result has made it easier to cope with my cancer</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note.** Distress subscale = Items 1–4, 7, and 8; Uncertainty subscale = Items 9–12, 14–17, and 20; Positive Experiences subscale (reverse scored) = Items 5, 6, 18, and 19. Subscales are scored by summing circled numbers.
A.4 Consent Form

UPMC
LIFE CHANGING MEDICINE

CONSENT TO USE MEDICAL RECORDS AND/OR QUESTIONNAIRES FOR RESEARCH IN THE UPMC Cancer Centers

PRINCIPAL INVESTIGATOR:
Randall Brand, MD. University of Pittsburgh.
Shadyside Medical Office Building
5200 Centre Avenue, Suite 409
Pittsburgh PA 15232
(412) 623-3135

ABOUT THE STUDY:
We are interested in understanding more about the genetic testing process for individuals with pancreatic cancer. In order to learn more, we would like to invite you to participate in a research study. The goal of this study is to collect information that will help doctors and genetic counselors better understand patients’ genetic knowledge and well-being after receiving either a traditional genetic counseling or video education. The type of education you receive is randomly selected. We plan to recruit 200 participants to the study.
Participation would involve the following three components:
1. Your completion of surveys
2. Permission to re-contact you over the phone at later dates
3. Permission to review your medical records

YOUR PARTICIPATION:
If you choose to participate you will be verbally asked questions during your office visit and asked to read some words out loud. These questions should take about 10 minutes to complete and will involve assessment of your genetic knowledge after receiving education. You will be randomized to receive either video education or a traditional genetic counseling with a genetic counselor. The video is approved for clinical use and has the same content as the in-person education. If you undergo genetic testing at your appointment, you will be contacted over the phone 2 weeks after disclosure of those test results and asked questions about your genetic knowledge and your perceptions of the genetic testing process; this phone call should take about 15 minutes. If you do not undergo genetic testing, you will not be contacted again by the study team. You will not be compensated for your study participation.

We are also requesting your permission to review your medical records for information about your medical history, cancer diagnosis and treatment, and family history of cancers. Information may be obtained from your medical records and used by this research team for an indefinite period of time. This authorization is valid for an indefinite period of time. However, you can always withdraw your authorization allowing the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. Any information obtained from you up to that point will continue to be used by the research team.
Per the University of Pittsburgh, all research records must be maintained for at least 7 years following final reporting or publication or a project.

Participation is completely voluntary and will not affect your care or management with UPMC or any affiliated organizations. Your doctor may be involved as an investigator in this research study, but you are not under any obligation to participate in any research study offered by your doctor. Before agreeing to participate in this research study, or at any time thereafter, you may wish to discuss participation in this study with another health professional to obtain a 'second opinion' about study participation. You are free to withdraw from the study at any time, for any
reason, without any penalty or change of care. However, any identifiable information obtained from you before you withdraw from this study will continue to be used by the investigators, as described above. You are also free to withdraw authorization for the research team to access your medical records, while still participating in the study. To formally withdraw your consent for participation in the study you should provide a written and dated notice to the primary investigator at the address above. The decision to withdraw consent from the study will have no effect on current or future medical care at a UPMC hospital or affiliated health care provider or the current or future relationship with a healthcare insurance provider.

CONFIDENTIALITY:
If you choose to participate in the study, your confidentiality will be protected and your personal identifying information will be coded with limited access. Your information will only be available to the research team, and possibly to auditors from the University of Pittsburgh Research Conduct and Compliance Office. There is always the small chance of a breach in confidentiality, but strong precautions and the federal confidentiality guidelines are followed to protect your information to the best of our abilities. If the researchers learn that you or someone with whom you are involved is in serious danger of harm, they will need to inform the appropriate agencies as required by Pennsylvania law. The research data collected may also be used for future unspecified research and shared in a de-identified manner with investigators both inside and outside of the University.

RISKS AND BENEFITS
There are no direct benefits to you involved in this study. The only risks associated with this study are the possibility of breach of confidentiality and distress associated with completion of questionnaires. There is no cost associated with this study, and neither you nor your insurance will be billed for study-related matters if you choose to participate. However, you will be responsible for standard clinical charges regardless of your participation in the study.

VOLUNTARY CONSENT:
This study has been explained to me, and all of my questions have been answered. Additional questions will be answered by the study team. The Human Research Subject Advocate of the University Institutional Review Board (1.866.212.2668) can answer any questions about my rights as a research subject. By signing this form, I give my authorization to share my medical records with the research team and answer their questions.

Patient/Subject Signature ___________________________ Date ___________ Printed Name of Patient/Subject ___________________________

I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

Signature of individual obtaining consent ___________________________ Date ___________
A.5 IRB Approval Letter

University of Pittsburgh
Institutional Review Board

APPROVAL OF SUBMISSION (Expedited)

<table>
<thead>
<tr>
<th>Date:</th>
<th>November 6, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB:</td>
<td>STUDY19040249</td>
</tr>
<tr>
<td>PI:</td>
<td>Randall Brand</td>
</tr>
<tr>
<td>Title:</td>
<td>Comparison of Traditional Genetic Counseling to Video Education in a Pancreatic Cancer Cohort Being Offered Genetic Testing</td>
</tr>
<tr>
<td>Funding:</td>
<td>None</td>
</tr>
</tbody>
</table>

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

<table>
<thead>
<tr>
<th>Review type:</th>
<th>Initial Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Date:</td>
<td>11/6/2019</td>
</tr>
</tbody>
</table>

Approved Documents:
- MICRA.pdf
- PDAC Genetics Knowledge Questionnaire
- REAL-G
- Video Consent

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Emily Bird.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.
Appendix B Data Outputs from Stata
### AGE DIFFERENCE BETWEEN EDUCATION GROUPS

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>38</td>
<td>37.5</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>67</td>
<td>67.5</td>
</tr>
<tr>
<td>combined</td>
<td>14</td>
<td>105</td>
<td>105</td>
</tr>
</tbody>
</table>

unadjusted variance 56.25
adjustment for ties -0.25

adjusted variance 56.00

Ho: Age(Educat~n==0) = Age(Educat~n==1)

\[ z = 0.067 \]

Prob > |z| = 0.9467

### SEX DIFFERENCE BETWEEN EDUCATION GROUPS

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>46</td>
<td>37.5</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>59</td>
<td>67.5</td>
</tr>
<tr>
<td>combined</td>
<td>14</td>
<td>105</td>
<td>105</td>
</tr>
</tbody>
</table>

unadjusted variance 56.25
adjustment for ties -17.31

adjusted variance 38.94

Ho: Sex(Educat~n==0) = Sex(Educat~n==1)

\[ z = 1.362 \]

Prob > |z| = 0.1732
DAYS BETWEEN DIAGNOSIS AND ENROLLMENT

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>27</td>
<td>37.5</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>78</td>
<td>67.5</td>
</tr>
<tr>
<td>combined</td>
<td>14</td>
<td>105</td>
<td>105</td>
</tr>
</tbody>
</table>

unadjusted variance 56.25
adjustment for ties -1.85

adjusted variance 54.40

Ho: Days(Educat~n==0) = Days(Educat~n==1)

\[ z = -1.424 \]

Prob > |z| = 0.1545

TIMEPOINT 1 KNOWLEDGE BY LITERACY LEVEL

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>LowLiteracy</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>54</td>
<td>52</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>combined</td>
<td>12</td>
<td>78</td>
<td>78</td>
</tr>
</tbody>
</table>

unadjusted variance 34.67
adjustment for ties -3.39

adjusted variance 31.27

Ho: Knowle~e(LowLit~y==0) = Knowle~e(LowLit~y==1)

\[ z = 0.358 \]

Prob > |z| = 0.7206
TIMEPOINT 1 KNOWLEDGE BY EDUCATION GROUP

```
ranksum Knowledge, by (Education)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>32</td>
<td>32.5</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>46</td>
<td>45.5</td>
</tr>
<tr>
<td>combined</td>
<td>12</td>
<td>78</td>
<td>78</td>
</tr>
</tbody>
</table>

unadjusted variance 37.92
adjustment for ties -3.71
adjusted variance    34.20

Ho: Knowle~e(Educat~n==0) = Knowle~e(Educat~n==1)
z = -0.085
Prob > |z| = 0.9319
```

TIMEPOINT 1 KNOWLEDGE BY LITERACY LEVEL (VIDEO GROUP)

```
Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>LowLiteracy</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>combined</td>
<td>7</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

unadjusted variance 6.67
adjustment for ties -0.60
adjusted variance    6.07

Ho: Knowle~e(LowLit~y==0) = Knowle~e(LowLit~y==1)
z = 0.406
Prob > |z| = 0.6849
DIFFERENCE IN DAYS BETWEEN TIMEPOINTS BY EDUCATION GROUP

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>15.5</td>
<td>27.5</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>39.5</td>
<td>27.5</td>
</tr>
<tr>
<td>combined</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance 22.92
adjustment for ties -0.69
adjusted variance 22.22

Ho: Days(Educat~n==0) = Days(Educat~n==1)

\[ z = -2.546 \]

\[ \text{Prob } |z| = 0.0109 \]

TIMEPOINT 2 KNOWLEDGE BY EDUCATION GROUP

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>32</td>
<td>27.5</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>23</td>
<td>27.5</td>
</tr>
<tr>
<td>combined</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance 22.92
adjustment for ties -2.78
adjusted variance 20.14

Ho: Knowle~2(Educat~n==0) = Knowle~2(Educat~n==1)

\[ z = 1.003 \]

\[ \text{Prob } |z| = 0.3160 \]
TIMEPOINT 2 KNOWLEDGE BY LITERACY LEVEL

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>LowLiteracy</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>combined</td>
<td>9</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

unadjusted variance 15.00
adjustment for ties -1.75
adjusted variance 13.25

Ho: Knowledge2(LowLit~y==0) = Knowledge2(LowLit~y==1)

\[ z = -0.275 \]

Prob > |z| = 0.7835

DIFFERENCE IN KNOWLEDGE SCORE BETWEEN TIMEPOINT 1 AND 2 (ALL)

Wilcoxon signed-rank test

<table>
<thead>
<tr>
<th>sign</th>
<th>obs</th>
<th>sum ranks</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>2</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>negative</td>
<td>7</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>zero</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>all</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance 96.25
adjustment for ties -7.00
adjustment for zeros -0.25
adjusted variance 89.00

Ho: Knowledge2 = Knowledge

\[ z = -1.378 \]

Prob > |z| = 0.1682
DIFFERENCE IN SCORE BETWEEN TIMEPOINT 1 AND 2 (GC GROUP)

Wilcoxon signed-rank test

<table>
<thead>
<tr>
<th>sign</th>
<th>obs</th>
<th>sum ranks</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>1</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>negative</td>
<td>3</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>zero</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>all</td>
<td>5</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

unadjusted variance 13.75
adjustment for ties -0.50
adjustment for zeros -0.25

adjusted variance 13.00

Ho: Knowledge2 = Knowledge
\[ z = -0.555 \]
\[ \text{Prob} > |z| = 0.5791 \]

DIFFERENCE IN SCORE BETWEEN TIMEPOINT 1 AND 2 (VIDEO GROUP)

Wilcoxon signed-rank test

<table>
<thead>
<tr>
<th>sign</th>
<th>obs</th>
<th>sum ranks</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>1</td>
<td>2.5</td>
<td>7.5</td>
</tr>
<tr>
<td>negative</td>
<td>4</td>
<td>12.5</td>
<td>7.5</td>
</tr>
<tr>
<td>zero</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>all</td>
<td>5</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

unadjusted variance 13.75
adjustment for ties -1.25
adjustment for zeros 0.00

adjusted variance 12.50

Ho: Knowledge2 = Knowledge
\[ z = -1.414 \]
\[ \text{Prob} > |z| = 0.1573 \]
MICRA SCORE BY EDUCATION GROUP

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>29.5</td>
<td>27.5</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>25.5</td>
<td>27.5</td>
</tr>
<tr>
<td>combined</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance = 22.92
adjustment for ties = -0.28

adjusted variance = 22.64

Ho: MICRA(Educat~n==0) = MICRA(Educat~n==1)

\[ z = 0.420 \]

Prob > |z| = 0.6742

DISTRESS SCORE BY EDUCATION GROUP

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>25.5</td>
<td>27.5</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>29.5</td>
<td>27.5</td>
</tr>
<tr>
<td>combined</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance = 22.92
adjustment for ties = -0.14

adjusted variance = 22.78

Ho: Distress(Educat~n==0) = Distress(Educat~n==1)

\[ z = -0.419 \]

Prob > |z| = 0.6752
UNCERTAINTY SCORE BY EDUCATION GROUP

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>33</td>
<td>27.5</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>22</td>
<td>27.5</td>
</tr>
<tr>
<td>combined</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance: 22.92
adjustment for ties: -0.28
adjusted variance: 22.64

Ho: Uncert~y(Educat~n==0) = Uncert~y(Educat~n==1)
   z = 1.156
   Prob > |z| = 0.2477

POSITIVE EXPERIENCES SCORE BY EDUCATION GROUP

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

<table>
<thead>
<tr>
<th>Education</th>
<th>obs</th>
<th>rank sum</th>
<th>expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>26.5</td>
<td>27.5</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>28.5</td>
<td>27.5</td>
</tr>
<tr>
<td>combined</td>
<td>10</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

unadjusted variance: 22.92
adjustment for ties: -1.25
adjusted variance: 21.67

Ho: Positive(Educat~n==0) = Positive(Educat~n==1)
   z = -0.215
   Prob > |z| = 0.8299
Appendix C List of Genes Analyzed

A complete list of genes analyzed as a part of Invitae’s Detect Study for Hereditary Pancreatic Cancer. For more information, please visit www.invitae.com.

AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPRI1A, BRCA1, BRCA2, BRIP1, CASR, CDC73, CDH1, CDK4, CDKN1B, CDKNIC, CDKN2A, CEBPA, CHEK2, CTNNA1, DICER1, DIS3L2, EGFR, EPCAM*, FH, FLCN, GATA2, GPC3, GREM1*, HOXB13, HRAS, KIT, MAX, MEN1, MET, MITF**, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RECQL4, RET, RUNX1, SDHA**, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1

*Deletion/duplication analysis only

** Sequence analysis only


